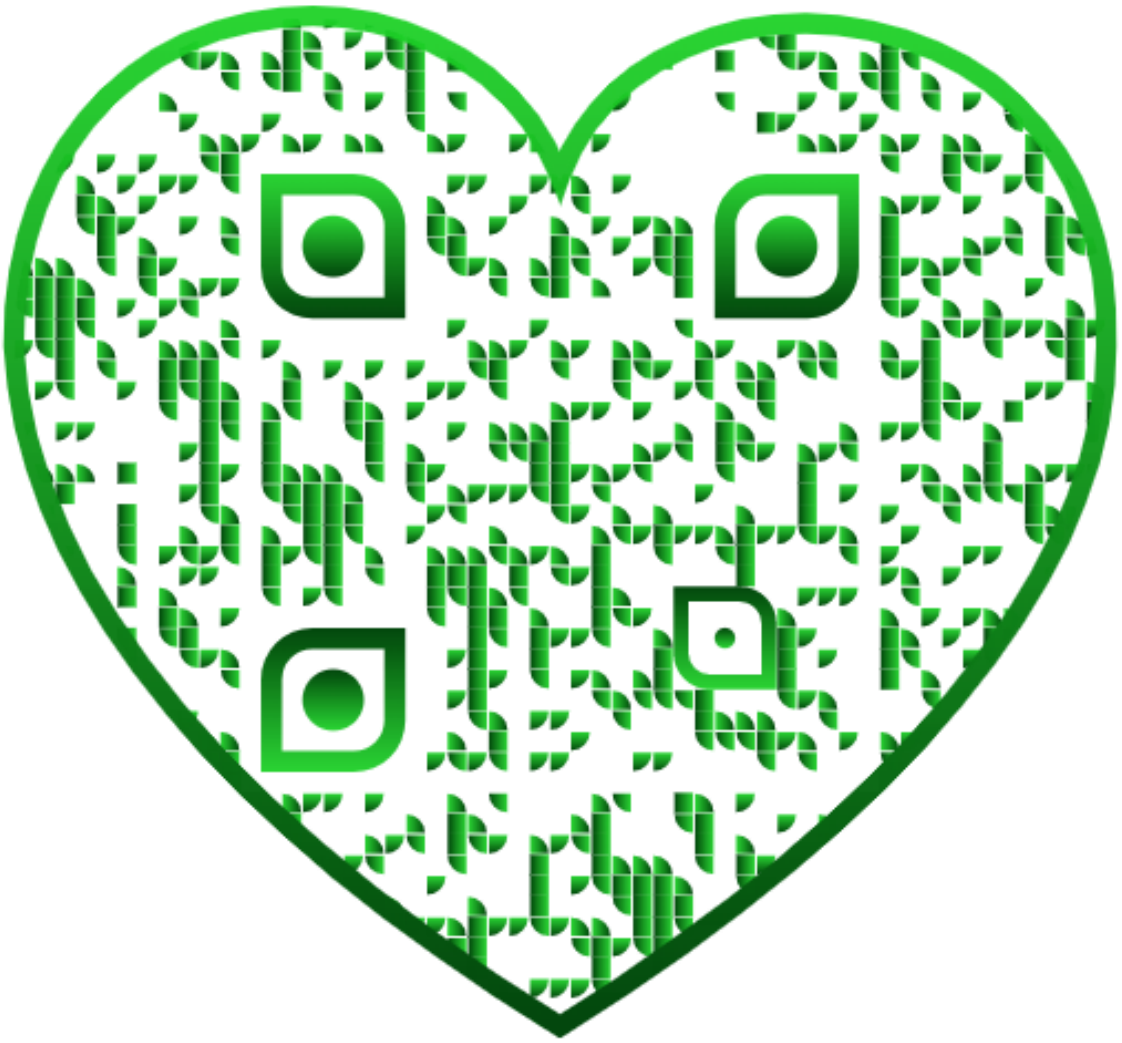
IPP-I-10

- Dosage Form Sciences Module
- **Module Number**: 09
- **Course Title**: Integrated Physical Pharmacy & Pharmaceutics- I
- **Course Code**: Phar 2091
- **Course weight** : 9 EtCTS or 243 hrs
- **Prerequisite**: Pharmaceutical Calculations
- **Lecture hours : 64**
- **Instructor: Tesfu Negussie**
- **Qualification:**
  - **MPH**
  - **MSc, BA, Bpharm**



Course synopsis

1. Introduction to Pharmaceutical excipients, dosage forms and routes of drug administration …….(3 hrs)
2. Phase Equilibria ……..(6 hrs)
3. Interfacial Phenomena ……(8 hrs)
4. Solubility and Distribution Phenomena ……..(9 hrs)
5. Packaging and storage of pharmaceuticals ….(5 hrs)
6. Pharmaceutical Solutions ……(8 hrs)
7. Rheology ……(7 hrs)
8. Colloids……(5 hrs)
9. Pharmaceutical Suspensions ..……(7 hrs)
10. Pharmaceutical Emulsions ……..(6 hrs)

Teaching Methodology

- ❖Lecture
- ❖Discussion

Assessment methods

- ❖Lab. Practice & report ……..…. 25%
- ❖Continuous Assessment ……..…… 35%
- ❖Final exam…… 40%

❖References

- Martin's physical Pharmacy & pharmaceutical sciences 5th edn
- Bentley's Text books of pharmaceutics
- Aulton,ph armaceutics the science of dosage form design

Unit 1: Introduction to Pharmaceutical excipients, dosage forms & routes of drug administration …(3 hr)

- Definition
- The need for dosage forms, classification
- Overview of dosage form design
- Introduction to pharmaceutical ingredients
- Routes of administration

1.1 Definition

- **Pharmaceutics** is a branch of pharmacy that is concerned with the scientific & technological aspects of design & development of dosage forms
- It is the most diverse of all the subjects in pharmaceutical science
- **Physical pharmacy** is a discipline in pharmacy that is concerned with the physical properties of pharmaceutical ingredients

1.2. Principles of dosage form design

Design of dosage form requires understanding of three principles

A. Biopharmaceutics aspects of dosage form design
   - Routes of drug administration

B. Drug related factors
   - Physicochemical properties of drugs & excipients

C. Therapeutic consideration of the disease state to be treated
   - Clinical indications of disease & patient factors

1.4. Factors affecting dosage form design

- Physicochemical properties of drug
- Physicochemical properties of dosage forms
- Routes of drug administration
- Clinical indications
- Patient factors

Physicochemical properties of drug & its dosage forms

Physicochemical properties of drug that influence dosage form design includes:

- ❖ Particle size
- ❖ Partition coefficient
- ❖ Polymorphism
- ❖ Stability
- ❖ Organoleptic properties

Particle size

- Finely divided particle have larger specific surface area[i.e, surface area per unit weight of powder] than course particles
- The former can be easily penetrated by solvent ,hence undergo dissolution at a faster rate as compared to later particles
- Faster absorption, thus rapid onset of action is secured from finely divided particles than larger particles

Partition coefficient[PC] : A measure of lipophilic character of a drug

$$PC = \frac{[\text{drug molecules in oil}]}{[\text{drug molecules in } H_2O]} \text{ or } \frac{[Drug]_{water}}{[Drug]_{oil}}$$

- Majority of drugs are weak organic bases or acids
  - ➢ Exist as ionized & non-ionized forms depending on pH of surrounding medium
- Unionized forms are more lipid soluble than ionized form, hence has faster absorption rate
- Ionized form can be bound to or repelled by charged nature of cell membrane

Result: Reduced drug penetration via cell membrane

Polymorphism

- Existence of drug substance in different crystal forms
- One of them is stable while the rests are metastable
- Both stable & metastable forms exhibits same chemical but different physical properties
- Metastable forms have higher dissolution rate than stable forms
- Metastable form converts to stable form during shelf-life, milling, granulating, drying & /or compression operation of polymorph

➢ Powdered polymorph —Granulation→ Solvation

➢ Solvated polymorph —Drying→ Anhydrous polymorph

Note: Formulator should notice such potential conversion

1.3. Types of dosage forms

Dosage form:

- drug delivery system designed to deliver active ingredient to the body
- delivers drug at a rate and amount that assures desired pharmacological effect
- produce the same therapeutic response each time it is administered
- can be categorized based on route of administration or physical forms

Classification based on physical form :

1. **Liquid dosage forms**(homogenous & heterogeneous systems)
   - Solution
   - Micro-emulsion
   - Nano-emulsion
   - micro-suspension
   - Nano-suspension
   - Emulsion
   - Suspension
2. **Semisolid dosage forms**
   - Ointment /Paste
   - Cream
   - Jellies
   - Transdermal patches

3. Solid dosage forms

- Powder
- Granules
- Pellets
- Tablets
- Capsules
- Suppository
- Pessary

1.4. Introduction to pharmaceutical excipients

- Any substance other than active drug or pro-drug that are evaluated for safety & used in a drug delivery system . Also known as inactive or inert ingredients
- Compounds that are added to pharmaceutical formulation for production of successful & acceptable dosage forms
- Major components of the drug product
- Used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients

General criteria for excipients

- Physiological inertness
- Maintain physical and chemical stability
- Conformance to regulatory agency requirements
- No interference with drug bioavailability
- Absence of pathogenic microbial organisms
- Cheap

Function of excipients varies substantially depending on individual dosage forms

General function of excipients

- Aid pharmaceuticals manufacture processes
- Protect, support, or enhance stability
- Enhance drug release from its dosage form, hence its bioavailability
- Assist in product identification
- Enhance any other attribute of overall safety and effectiveness of drug product during storage and use

1.4.1. Pharmaceutical solvents

- Aqueous solvents
- Nonaqueous solvents

i. Aqueous solvents

- Purified water
- Water for injection
- Sterile water for injection
- Bacteriostatic sterile water for injection

Purified water

- Any water subjected to certain level of purification

  Example

  - ❖ Distilled water
  - ❖ Demineralized water
  - ❖ Soft water
  - ❖ Filtered water

- Used for topical & oral dosage form preparation

Water for injection [WFI]

- Purified water subjected to steam distillation or reverse osmosis
- Free from pyrogen & particulate matter
- May not be necessarily sterile
- Used to prepare terminally sterilizable injectable

Sterile water for injection

- Individually filled as a single dose [≤ 1 lt]
- Terminally sterilized WFI
- Used for reconstitution of multiple dose medicine

Bacteriostatic WFI

- Sterile WFI containing antimicrobial agents

ii. [non-water solvents]

- Used for drugs having limited water solubility or susceptible to hydrolysis

Example - **Non-aqueous solvents** :

- Fixed vegetable oil such as corn oil
- Glycerine
- Propylene glycol

Criteria for nonaqueous solvents

- Non-irritant, nontoxic & non-sensitizing
- Should never affect drug activity
- Have optimal viscosity that permits its use in syringe
- Maintain its fluidity over wider range of temperature
- Their b.p & vapour pressur should let terminal sterilization of end products
- Must be miscible with body fluids

1.4.2. Preservatives

Compounds that are used to inhibit microbial triggered pharmaceuticals instability

Examples	Mechanisms of antimicrobial Action
Benzoic acid	Denaturation of protein
Boric acid	Denaturation of protein
Phenol	Denaturation &lytic of cytoplasmic membrane
Alcohol	Denaturation &lytic of cytoplasmic membrane

Criteria for selection of effective antimicrobial preservatives

- Have broad spectrum antimicrobial activity
- Have adequate concentration in aqueous phase
- Remain undissociated at pH of the preparation
- Create no inconvenience during drug administration
- Stable through out shelf-life of the product
- Compatible with formulation ingredients , containers & closures

Mechanism of action of preservatives

Interfere with microbial growth, multiplication &/or metabolism, as follow:

- Partial lysis of microbial cell membrane
- Lysis & cytoplasmic leakage
- Increase cellular permeability to cell constituents
- Microbial protein precipitation[irreversible coagulation of cytoplasmic constituents]
- Inhibition of cellular metabolism
- Preclude cell wall synthesis & enzyme activities
- Oxidation & /or hydrolysis of cellular constituents

1.4.3. Antioxidants

- Used to prevent oxidation of drugs and excipients in the finished product.
- There are three main types of antioxidants:
- **True Antioxidants**: act by a chain termination mechanism by reacting with free radicals

  e.g., Butylated hydroxytoluene[BHT], BH-Anisole [BHA]
- **Reducing Agents**: have a lower redox potential than the drug and get preferentially oxidized, Thus, they can be consumed during product shelf-life

  e.g., Ascorbic acid
- **Antioxidant Synergists**: Enhance effect of antioxidants e.g., EDTA.

Note

- Water soluble antioxidants act preferentially by undergoing oxidation in place of the drug

Example

- Sodium sulphite
- Sodium metabisulfite
- Ascorbic acid

- Oil soluble antioxidants serve as free radical acceptor & inhibit free radical chain process

Example : BHT , BHA

Inhibition of propagation process of Autoxidation

- Propagation of chain process requires formation of free radicals[R·, RO· Or ROO·]
- Antioxidant molecule[AH] reacts with free radical to form free radical A·
- AH + R· ⟶ RH + A· **Or** AH + Roo· ⟶ ROOH + A·
- The formed free radical A. is not sufficiently reactive to sustain chain process

Result: Antioxidant radical is annihilated by combining with another antioxidant radical or free radical

A· + A· ⟶ AA or A· + R· ⟶ AR

Note

- Chemical bond of antioxidant compound should be weaker than that of autoxidizable substances to ensure effective stabilization
- Antioxidant reacts with atmospheric oxygen faster than oxidizable drug molecules there by retards onset of Autoxidation of drug molecule

$$AH + O_2 \longrightarrow A. + H_2o$$

- More free radicals are formed in a partially oxidized formulation, thus unless adequate quantities of antioxidants are added to such formulation, they will be rapidly consumed up

Properties of ideal antioxidants

- Effective at low concentration
- Adequately soluble in oxidizable products
- Non-toxic & non-irritant at effective concentration
- Never impart colour to the product
- Its decomposition product should be non-toxic & non-irritant
- Stable & effective over a wide range of pH
- Neutral & compatible with other formulation ingredients
- Have low level of volatility

1.4.4. Buffer solutions & pH adjusting agents

Buffer solutions: solutions containing weak acid or base & their corresponding conjugates

or

- A buffer can be defined as a solution that maintains ≈ equal pH value even if small amounts of acidic or basic substances are added.
- To function in this manner, a buffer solution will necessarily contain either an acid and its conjugate base, or a base and its conjugate acid.

- Majorities of drugs are weak organic acids or bases, hence their solubility is pH dependent
- However addition of buffer solution resists slight change in pH upon introduction of small quantities of acid or base due to their inherent buffer action
- In a solution where buffer action is absent or inadequate, pH can change considerably via absorption of CO_2 from air or extraction of alkali from immediate containers such as glass

Mechanism of action of buffer solution

- Consider buffer solution formed from Acetic acid & Sodium acetate

$$CH_3COOH + NaOH \rightleftharpoons CH_3COONa + H_2O$$

$$CH_3COONa + HCL \rightleftharpoons NaCl + CH_3COOH$$

$$pH = -\log[H+] = pKa + \log[\frac{salt}{acid}]$$

Example: What is the pH of 20 ml buffer solution prepared by mixing 5 ml of N/100 acetic acid [pKa = 4.76] with 15 ml N/10 sodium acetate ?

Solution:

$$[CV]_1 = [CV]_2$$

$[salt] = [15 \text{ ml} \times 0.1N]/20 \text{ ml} = 0.075 \text{ N} = C_2$ of salt

$[acid] = [5 \text{ ml} \times 0.01]/20 \text{ ml} = 0.0025 \text{ N} = C_2$ of acid

$pH = pKa + \log[salt]/[acid]$

$= 4.76 + \log[0.075/0.025]$

$= 5.24$

Note: Buffers have maximum buffer capacity near their pKa

Criteria for selection of a buffer

Buffer must :

- have adequate buffering capacity in the desired pH range
- permit acceptable flavouring & colouring of the product
- not have deleterious effect on stability of final product

1.4.5. Viscosity inducing [Thickening] agents

- Substances that increase viscosity of liquid

  Example

  - HPMC
  - Polyvinyl alcohol
  - MC

- Viscosity [η] refers to resistance to flow
- Viscosity is inversely related to temperature
- Its reciprocal is called fluidity [$1/\eta$ = fluidity]

1.4.6. Surfactants& emulsifying agents

- **Surfactants** are substances which, at low concentrations, adsorb onto surfaces or interfaces of a system and alter the surface or interfacial free energy and tension
- Surface-active agents have both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. Thus, they are **amphipathic [**zwitterionic] in nature
- The lipophilic region tends to expelled from bulk of polar liquid while the hydrophilic region inhibit SAA from being completely expelled from polar region
- Therefore, balance should be kept b/n polar & non-polar regions of SAAs for reliable adsorption of hydrophilic region in aqueous phase & lipophilic region in non-aqueous phase

Types of SAAs based on charges of hydrophilic region

- Anionic Surface Active Agents
- Cationic Surface Active Agents
- Non-ionic Surface Active Agents

Anionic Surface Active Agents

➢Has negatively charged hydrophilic group

Example; Sodium lauryl sulfate , Sodium dodecyl sulfate, Sodium stearate

Cationic Surface Active Agents

- Hydrophilic group bears positive charge

Example : Cetyl trimethyl ammonium bromide

Benzalkonium chloride

Nonionic Surface Active Agents: Bear ester or ether group, no charge on their hydrophilic region

Example:

- Tweens [high HLB values], used to emulsify O/W emulsion
- Spans [low HLB values] ,used to emulsify W/O emulsion

Emulsifying agents [Emullgent or emulsifier]

- Compounds that form film on globules at the interfaces to reduce interfacial tension

Example : Acacia , Tragacanth, Gelatin, etc

Properties of ideal emulsifier

- Compatible with other formulation ingredients
- Stable during shelf-life of the finished products
- Promote effective emulsification
- Keep emulsion stable during its shelf-life
- Non toxic

1.4.7. Organoleptic agents

Enhance product appearance & elegance , taste and smell

Example: Colorant, Sweetener, Flavor

1.4.8. Others

Excipients	Function	Example
▪Binder	Enhance powder aggregation in to granules	Starch past, povidone soln, gelatin solution
Disintegrant	Facilitate water up-take by tablet or capsule	Dried starch, Na-starch glycolate
Lubricant	Reduce interfaces friction	Mg-stearate, Talc
Anti-adherent	Prevent adhesion of granules	Talc
Glidants	Promote flow of granules	Talc

Quiz: **Write true or false & give reasons for each answers.**

1. The metastable form of drug-x is dissolution rate limited compared to its stable form since the former is more crystalline than the later
2. All oxidizable substances have equal oxidation potential; that is why sodium bisulphite is preferentially oxidized prior to the drug
3. Water for injection is used for reconstitution of procaine penicillin prior to intramuscular administration
4. In a given buffer solution, its two species react with either the acid or the base but not both
5. Preservative that has larger water-in-oil partition coefficient is more effective than preservative that has larger oil-in-water partition coefficient

Unit 2: Phase Equilibria (6 hrs)

2.1. Introduction to intermolecular force of interaction

2.2. The phase rule

2.3. Phase equilibria of single, two and three component systems (principles and applications)

2.1. Introduction to intermolecular force of interaction

- They are forces that make molecules of gases, liquids and solids to exist in aggregate as a pure substances
- Cohesion and adhesion forces are manifestations of intermolecular forces
- Understanding of intermolecular forces help to comprehend:
  - ❖properties of pure substance[gas, liquids, solids]
  - ❖interfacial phenomena
  - ❖flocculation in suspensions
  - ❖stabilization of emulsion
  - ❖compaction of powder in capsules
  - ❖ compression of granules to form tablets

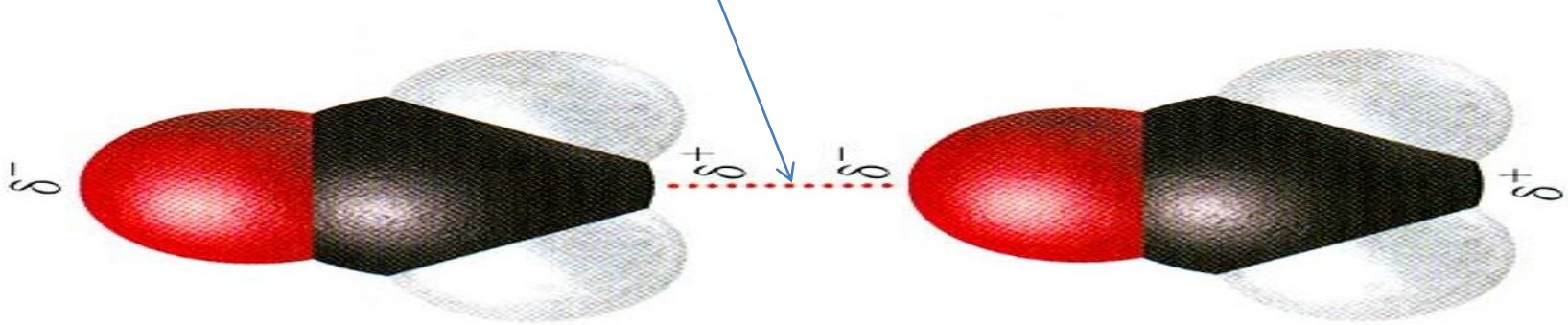
Types of intermolecular forces

1. Repulsive forces
2. Attractive forces
   A. Van der Waals forces
   B. Ion-dipole forces
   C. Ion-induced dipole forces

Repulsive and attractive forces

- Both forces operate when molecules interact
- Attractive forces are important for molecules to cohere while repulsive forces are necessary for prevention of molecular interpenetration and annihilation of one another
- Repulsion is due to interpenetration of electronic clouds of molecules & increase exponentially with a decrease in distance between molecules
- Both forces are equal at about $3\text{-}4x10^{-8}$ cm where potential energy b/n two molecules is a minimum and the system is most stable

- Intermolecular attractions are not nearly as strong as intra-molecular attractions that hold compounds together & determine their chemical properties
- They are, however, strong enough to control physical properties such as boiling, melting points, vapor pressures, viscosities, etc.
- These intermolecular forces as a group are referred to as Van der Waals forces



Van der Waals forces: Weak attraction forces responsible for alignment of **dipolar molecules** so that negative pole of one molecule points toward the positive pole of the next. The magnitude of these forces will increase as the distance b/n adjacent surfaces decreases. Responsible for condensation of gaseous molecules to liquids.

Types:

1. Induced dipole- induced dipole interaction [London forces] : Dispersion effect
2. Dipole-dipole interaction forces [Kessom forces]: orientation effect
3. Dipole-induced dipole interactions [Debye force] : Induction effect

Induced dipole- induced dipole interaction : **Dispersion forces [London forces]**

- They are attractions b/n an instantaneously induced-dipole and induced-dipole.
- Present in *all molecules,* whether they are polar or nonpolar
- Their strength tends to increase with increased molecular weight
- Larger atoms have larger electron clouds & hence easier to polarize

Substance	Boiling point	Melting point
n-pentane, C_5H_{12}	**36**	**-130**
n-nonane, C_9H_{20}	**151**	**-54**

- The magnitude of dispersion force depends on how easily atomic or molecular electrons can move or polarize in response to an instantaneous dipole that in turn depends on the size of the electron cloud.
- **Larger electron cloud** results in **greater dispersion force** as electrons are held less tightly by nucleus and hence can polarize [form dipole moment] easily
- If all other factors are constant, dispersion force increases with increasing molar mass

Example:

- Which halogen has higher bp: Cl_2 or I_2?
- Which molecule has higher bp? CH_4 or C_2H_6?

2.Dipole-Dipole Interaction[Kessom forces]:Orientation effect

- Exist in all polar molecules that have permanent dipoles
- The positive end of one is attracted to the negative end of the other and vice versa.
- Thus, polar molecules exhibit both **dipole-dipole interactions and London forces**
- This additional force raises their mp and bp relative to nonpolar molecules of same molar mass
- For instance formaldehyde is polar & hence has higher m.p. & b.p. than nonpolar ethane, even though the two compounds have the same molar mass [30 g/mole]

  Examples: Methanol , Ethanol

Which molecules have dipole-dipole forces? CH_4 , CH_2Cl_2 or CO_2

Which has a greater effect:

Dipole-dipole interactions or dispersion Forces?

- If two molecules are of comparable size and shape, dipole-dipole interactions will likely be dominating force to determine their physical properties
- If one molecule is much larger than another, dispersion forces will likely determine its physical properties

3. Dipole-induced-dipole interactions [Debye force] : Induction effect

- Produced by permanent dipoles that induce electric dipole in easily polarisable nopolar molecules via Induction effect

Hydrogen bonds

- Hydrogen bonding is a special type of molecular attraction between the hydrogen atom in a polar bond and nonbonding electron pair on a nearby small electronegative ion or atom (usually F, O or N)
- There is hydrogen bond b/n some alcohol, carboxylic acids, aldehydes, esters & polypeptides
- Acetic acid and formic acid [HCOOH] form their own dimers via hydrogen bond
- Hydrogen bonds are intermolecular forces while chemical bonds are inter-atomic bonds within the molecules

Note:

1. Hydrogen bond is responsible for unusual properties of H_2O such as high dielectric constant, abnormally low vapor pressure and high bp.
2. Dispersion force < Dipole-induced dipole force [Debey force < dipole-dipole force [Kessom forces] < hydrogen bond < Chemical bond

4. Ion -dipole forces

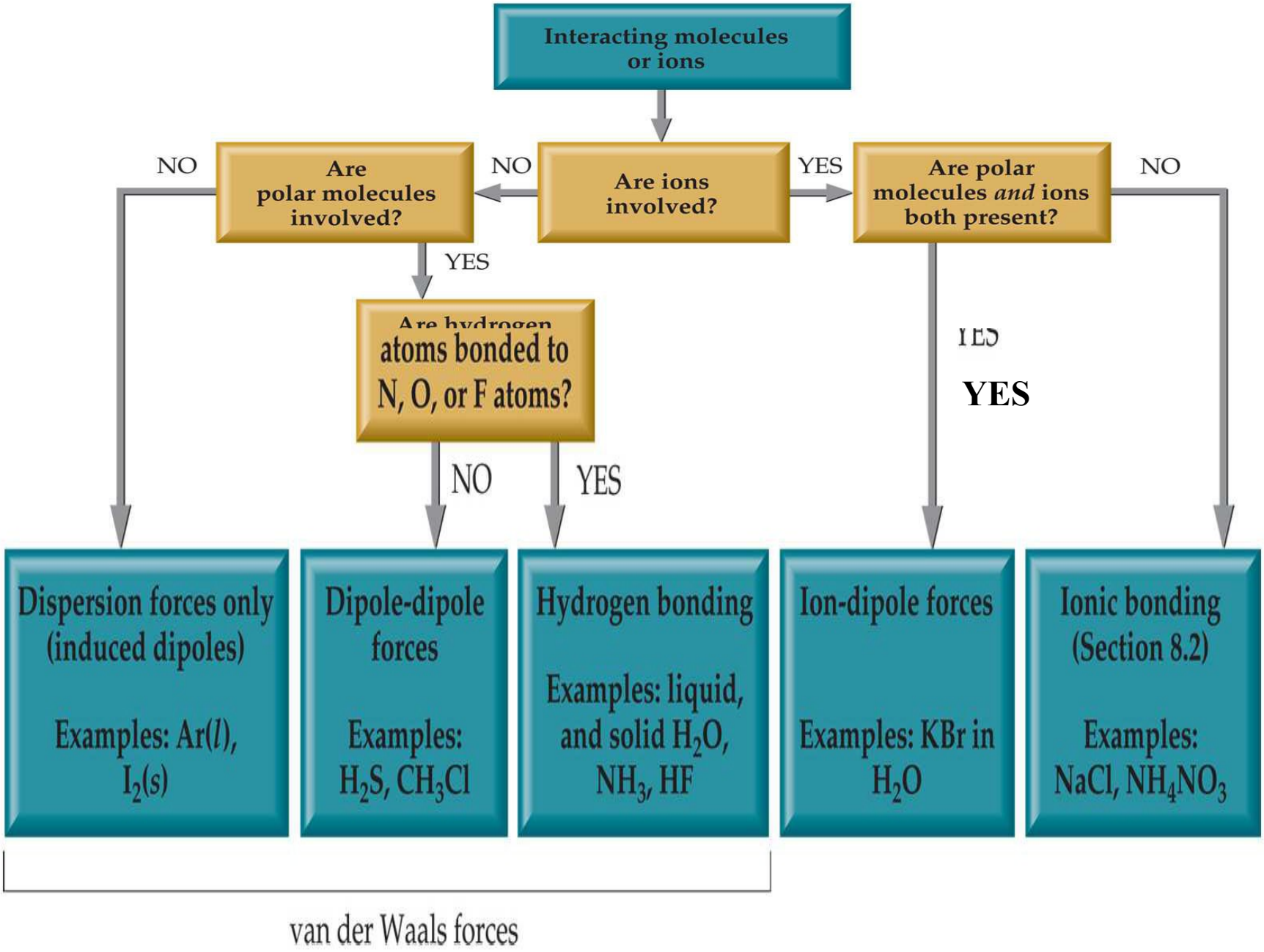
- Accounts for solubility of ionic crystalline substances in water such that cation attracts negatively charged oxygen and anion attracts positively charged hydrogen of water molecules.

Example: $NaCl + H_2O \longrightarrow NaOH + HCl$

5. Ion-induced dipole forces

- Formation of iodide complex to facilitate solubility of iodine in solution of KI is via ion-induced dipole forces

$$I_2 + K^+I^- \longrightarrow K^+I_3^-$$


Interacting molecules or ions
Are ions involved?
NO
Are polar molecules involved?
YES
Are polar molecules *and* ions both present?
NO
YES
YES
Are hydrogen atoms bonded to N, O, or F atoms?
NO
YES
Dispersion forces only (induced dipoles)
Examples: Ar(*l*), $I_2(s)$
Dipole-dipole forces
Examples: H_2S, CH_3Cl
Hydrogen bonding
Examples: liquid, and solid H_2O, NH_3, HF
Ion-dipole forces
Examples: KBr in H_2O
Ionic bonding (Section 8.2)
Examples: NaCl, NH_4NO_3
van der Waals forces

Note

- A phase is held together by intermolecular bonds that hold molecules in association & proximity with each other
- These bonds could be Van der Waals, ionic, dipole, or hydrogen bonds—depending on the atomic structure of the molecules of a phase.
- Water molecules are held together predominantly by hydrogen bond & dipole forces, whereas octane molecules are held together by weak Van der Waals forces
- These intermolecular forces of attraction and the proximity of the molecules follows the general trend: solids > liquids > gases

2.2. Phase rule

Used to relate effect of independent variables [pressure, concentration, Temperature,] upon various phases [gas, liquid & solid] that can exist in an equilibrium system containing a given № of components.

Gibb's phase rule: F = C- P + 2 , Where

F= **degrees of freedom** refers to the № of independent variables that must be fixed to completely determine the system

P= № of phases

Phase is a homogeneous, physically distinct portion of a system that is separated from other portion of a system by bounding surfaces

Eg: System containing water & its vapor is a two phase system while an equilibrium mixture of ice, liquid water and its vapor is a three phase system

№ of components, C is the smallest № of constituents by which composition of each phase in a system at equilibrium can be expressed in the form of chemical formula or equation

Example:

- In the system containing mixture of the three states of water, C= 1 since all are represented by H_2O
- In the three phase system, $CaCO_3 = CaO + CO_2$, the composition of each phase can be expressed by a combination of any two of the chemical species present

Thus, if we want to use , $CaCO_3$ & CO_2, we can write CaO as $CaCO_3 - CO_2$. Thus, C= 2

Example: Determine 'F' for the followings

1. Liquid water + vapor
2. Liquid ethyl alcohol + Vapor
3. Liquid water + Liquid ethyl alcohol + Vapor mixture
4. Liquid water + Liquid benzyl alcohol + Vapor mixture

Note: Ethyl alcohol &water are completely miscible both as liquids & vapours while benzyl alcohol and water form two separate liquid phases since they are partially miscible. Thus two variables are defined in the Ethyl alcohol &water system while only one variable in the benzyl alcohol & water system

- Gases are miscible in all proportions

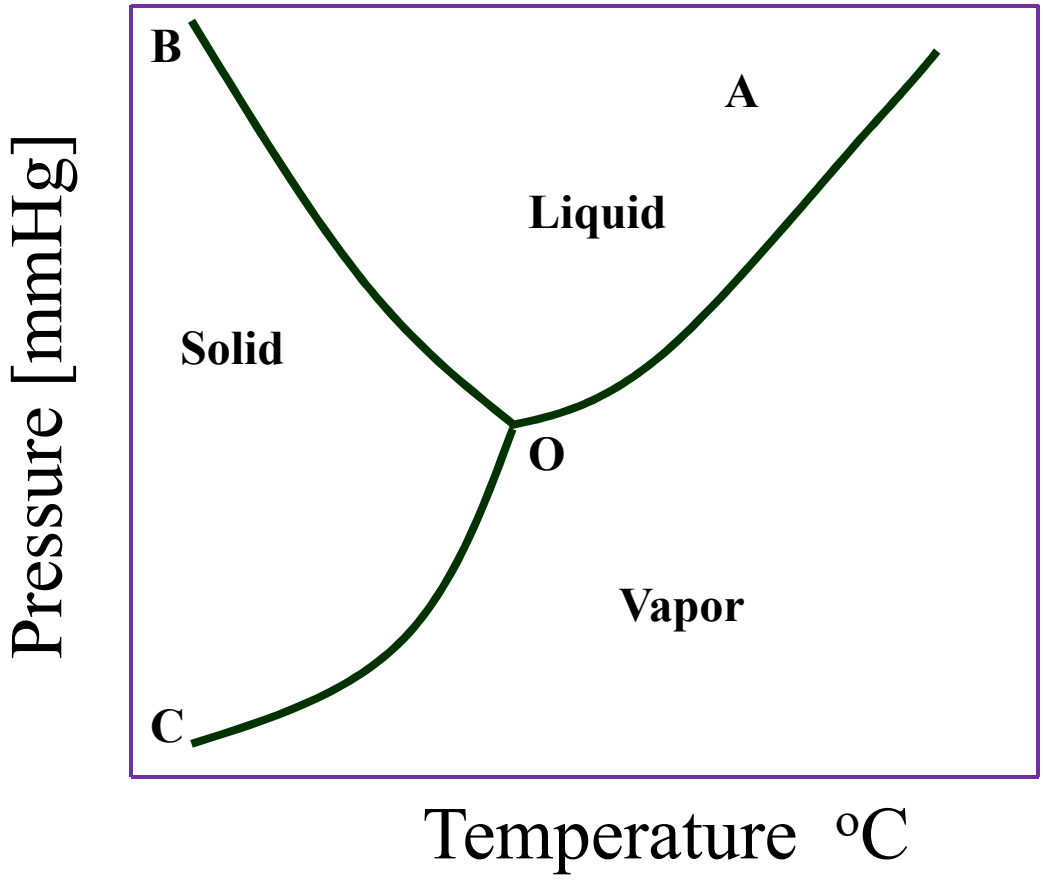
Answer: Q1, 2 & 4 . F=1; Q3. F= 2

2.3. Phase equilibria

- It describes the way phases (such as solid, liquid and/or gas) co-exist at some temperatures and pressure, but interchange at others
- A phase is a component within a system, existing in a precisely defined physical state, e.g. gas, liquid, or a solid that has a single crystallographic form
- A phase diagram is a graph showing values of applied pressure and temperature at which equilibrium exists
- A phase boundary is a line on a phase diagram representing values of applied pressure & temperature at which equilibrium exists
- The triple point on a phase diagram represents the value of pressure and temperature at which three phases coexist at equilibrium

- **Phase equilibria of :**
  - **One component system**
  - **Two component system**
  - **Three component system**

- **Phase equilibria of one component system**



Phase diagram for pure water

- **Phase equilibria of two component system**
    A. Containing liquid phases
    B. Solid & liquid phases

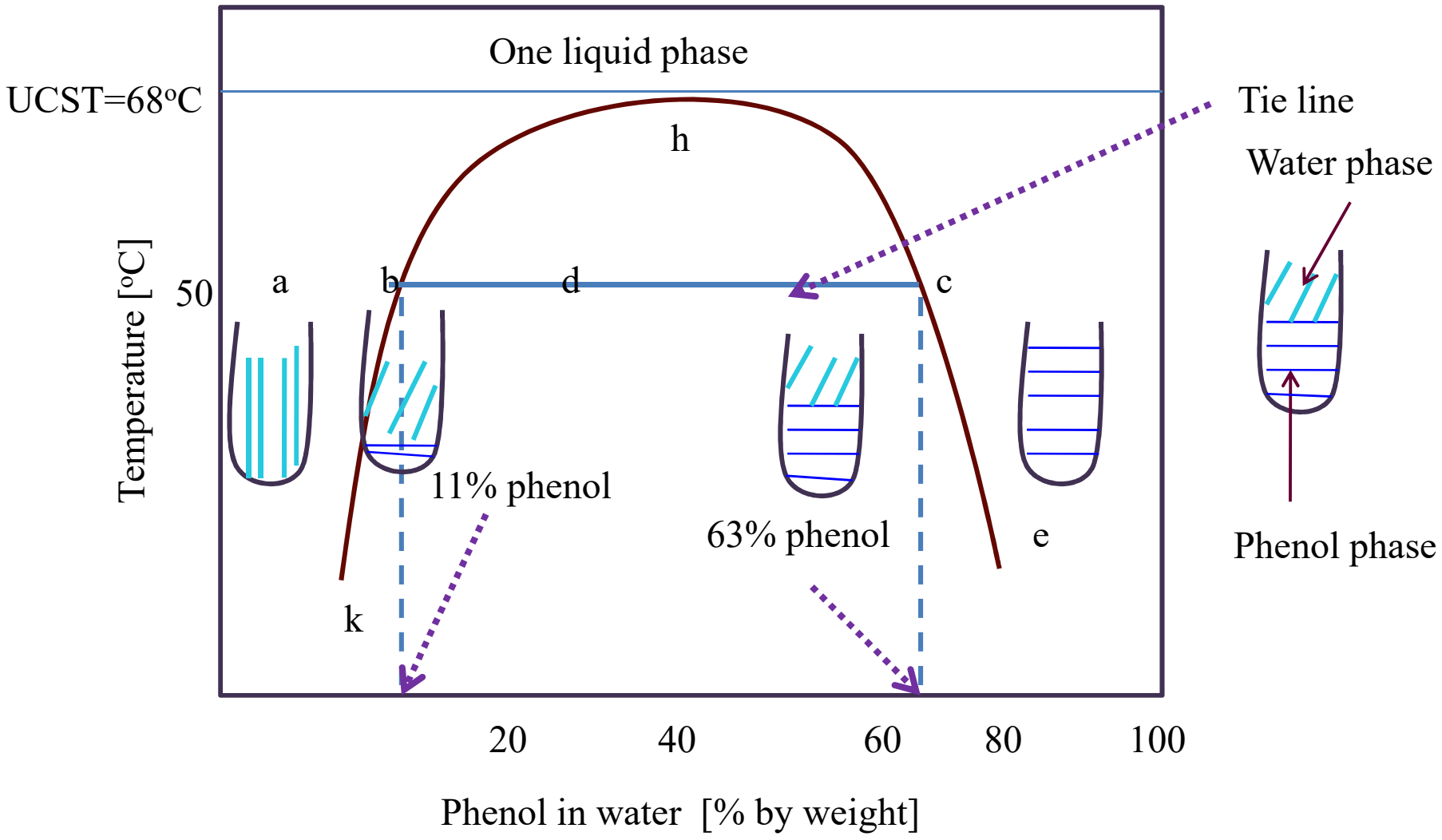
Phase equilibria of two component system containing liquid phases

- In a two component system, solid, liquid & vapor phases exist with a maximum of three degrees of freedom: Temperature, pressure & concentration.
- Its phase diagram needs using three dimensional model rather than the planar figure
- **Condensed system**: systems in which the vapor phase is ignored & only solid &/or liquid phase are considered so that the № of degrees of freedom is reduced to two

Example:

- Phenol -in- water, for which a condensed phase diagram is plotted on the next slide
- For phenol-water phase diagram, the binodal curve 'kbhce' shows the limit of temperature & concentration within which two liquid phases exist in equilibrium. The region outside this curve, contains systems having one liquid phase

Temperature –composition diagram for the system consisting of water and phenol



The tie line (Length bc)

- Drawn across the region that contain 2 phases
- Always parallel to abscissa in a two component systems
- All systems prepared in a tie line at equilibrium, will separate into phases of constant composition called conjugate phases
- Used to determine both composition and weight of each conjugate phases:

$$\frac{Weigh\ of\ phase\ \ A}{Weight of\ phase\ \ B} = \frac{length\ \ dc}{length\ \ db}$$

- It is also convenient to use units of percent weight of phenol as presented on abscissa:

$$\frac{Weigh\ of\ phase\ \ A}{Weight of\ phase\ \ B} = \frac{\%\ weight\ at\ point\ c - \%\ weight\ at\ point\ d}{\%\ weight\ at\ point\ \ d - \%\ weight\ at\ point\ b}$$

Example-1 : Assume that a liquid system weighing 10 g is prepared at 50 ^{0}C such that at point **d**, after equilibrium is established, each phase contains 24% by weight of phenol & 76% by weight of water.

Required:

1. Compute the phase[mass] ratio at point 'd' on the tie line
2. Weight of each phase
3. Composition of each phase

Solution:

1. Phase ratio at point 'd' on the tie line

$$\frac{Weigh\ of\ phase\ A}{Weight of\ phase\ B} = \frac{\%\ weight\ at\ point\ c - \%\ weight\ at\ point\ d}{\%\ weight\ at\ point\ d - \%\ weight\ at\ point\ b}$$

$$= [63\% - 24\%]/ [24\% - 11\%]$$

$$= \underline{3:1}$$

2. Weight of each phase

i. Weight of phase 'A' = 3 [Weight of phase 'B']

= 10 g x 3 parts / 4 parts

= 7.5 g

ii. Weight of phase 'B' = 10 g – 7.5 g = 2.5 g

3. Composition of each phase

i. Composition of phase 'A'

Phenol composition of phase 'A' = 24% x weight of phase 'A'

= 0.24 x 7.5 g = 1.8 g phenol

Water composition of phase 'A' = 76% x weight of phase 'A'

= 0.76 x 7.5 g = 5.7 g

ii. Composition of phase 'B'

Phenol composition of phase 'B' = 24% x weight of phase 'B'

= 0.24 x 2.5 g = 0.6 g phenol

Water composition of phase 'B' = 76% x weight of phase 'B'

= 0.76 x 2.5 g = 1.9 g water

Example-2

Suppose that 24 g of phenol is mixed with 76 g of water at 50 ^{0}C to form a phenol-water system which is kept at equilibrium at same temperature. Later on phase 'A' & 'B' are separated at same temperature so that 75 g & 25 g of phase 'A' & 'B' contain 11% and 63% by weight phenol, respectively.

Required: Determine amount of phenol & water in each phase.

Solution:

Amount of phenol in phase 'A' = 11% x weight of phase 'A'

= 0.11 x 75 g = 8.25 g

Amount of phenol in phase 'B' = 63% x weight of phase 'B'

= 0.63 x 25 g = 15.75 g

Amount of water in phase 'A' = 89% x weight of phase 'A'

= 0.89 x 75 g = 66.75 g

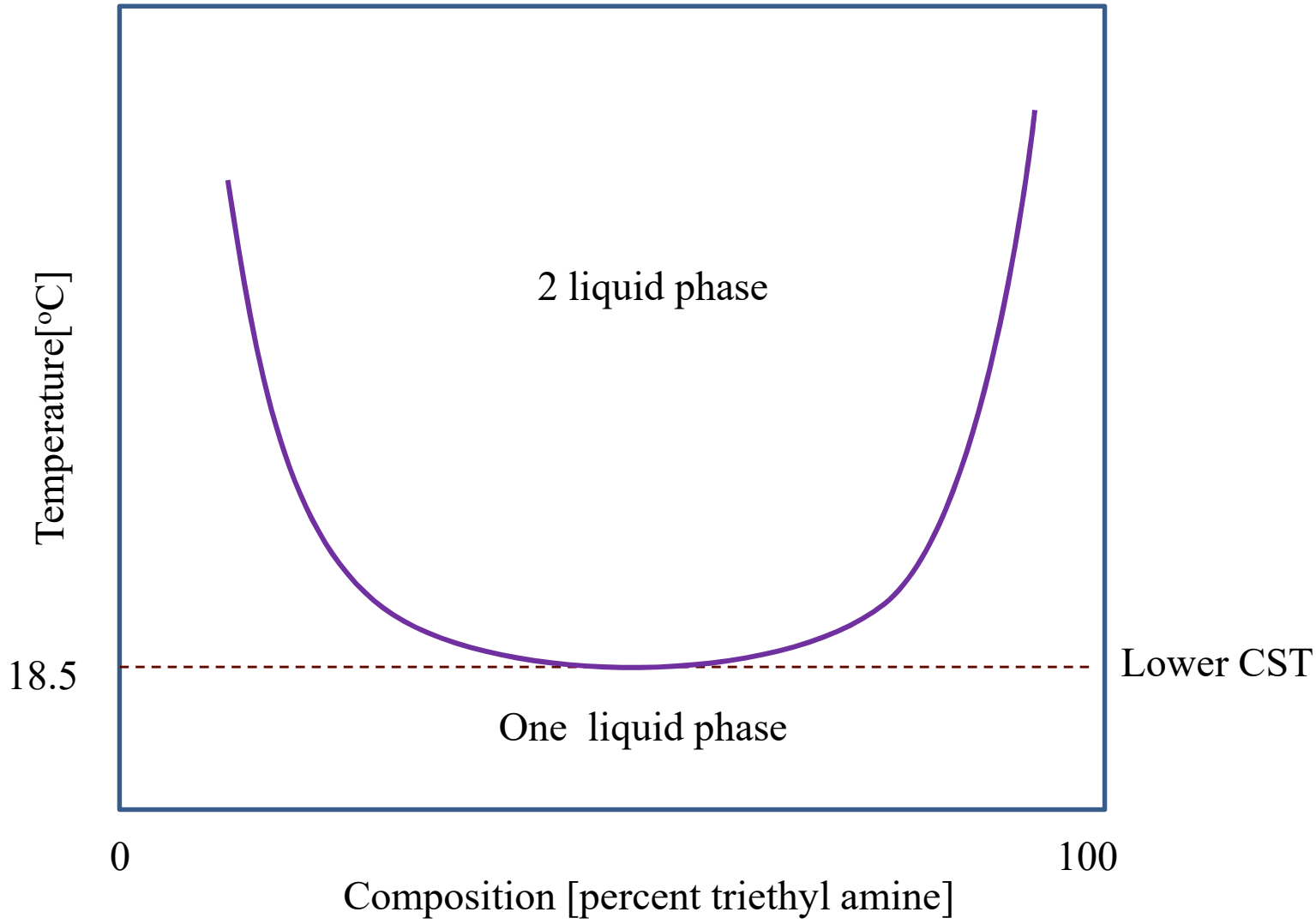
Amount of water in phase 'B' = 0.37% x weight of phase 'B'

= 0.37 x 25 g = 9.25 g

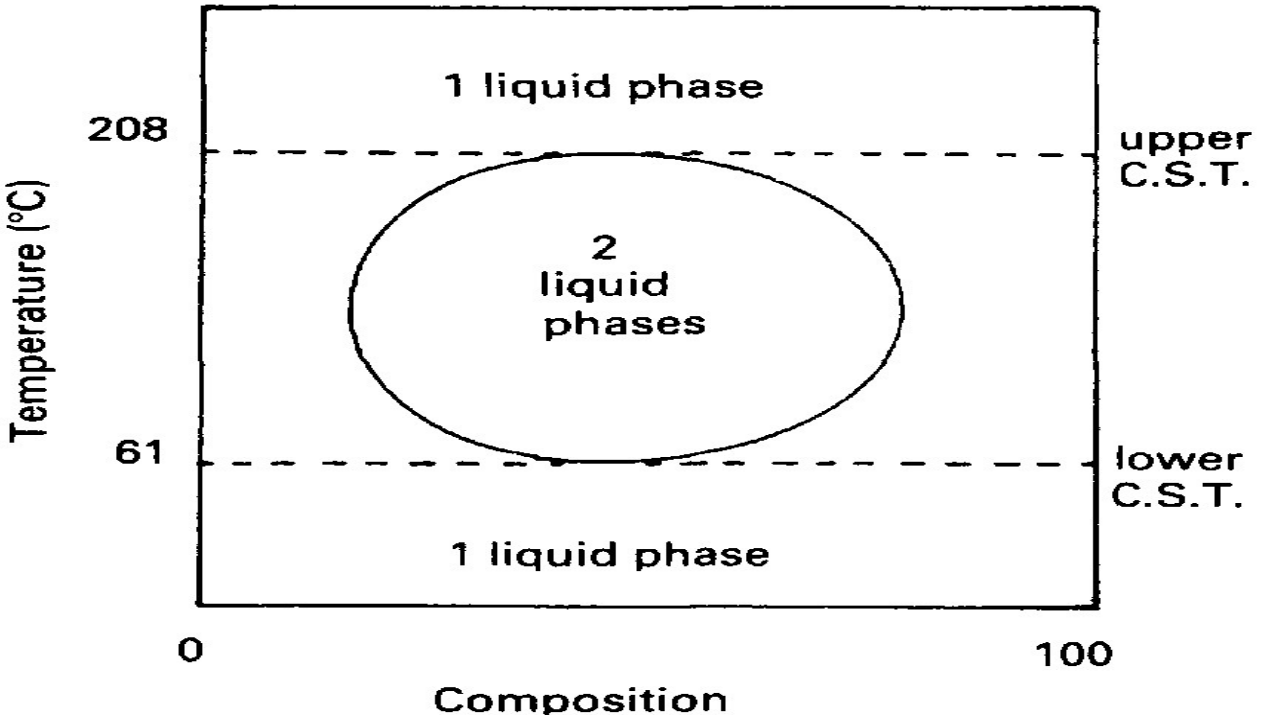
Exercise

- A mixture of phenol & water at 20 ^{o}C has a total composition of 50% phenol. The tie line at this temperature cuts the binodal at points equivalent to 8.4% & 72.2% w/w phenol. What is the weight of aqueous & phenol layers in 500 g of the mixture & how many grams of phenol are present in each of the two layers?

Temperature-composition diagram for the triethylamine-water system (at 101 325 kPa, standard atmospheric pressure).



Temperature-composition diagram for the nicotine- water system (at 101 325 kPa; standard atmospheric pressure).



Note: The pair ethyl ether & water has neither UCT nor LCT showing partial miscibility over entire temperature range at which the mixture exists

- **Phase equilibria of two component system in** Solid & liquid phases: Eutectic mixtures

Example Salol, thymol, camphor, phenol, menthol& chloral hydrate

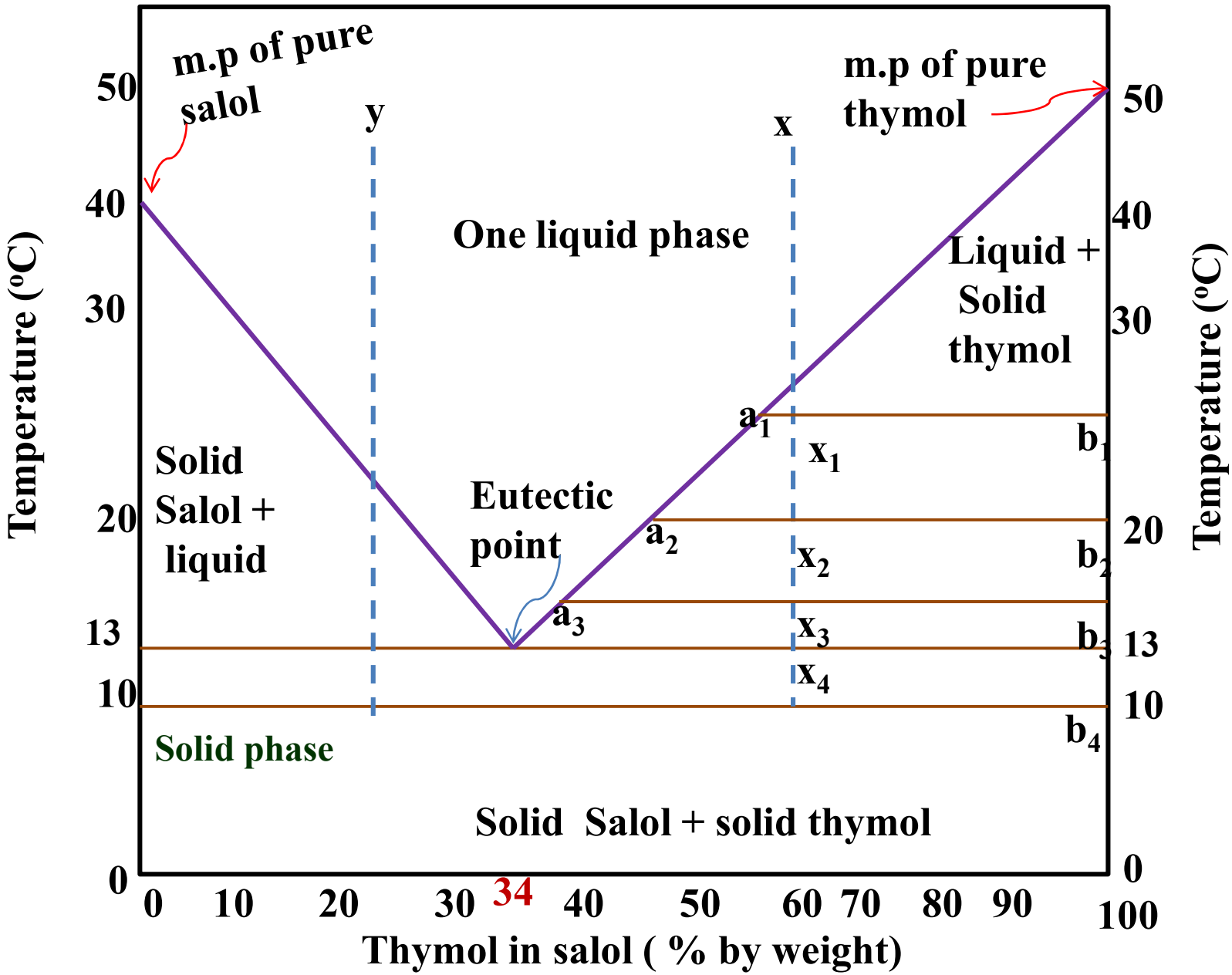
Combination of any two from the above lists form a mixture in which two components are completely miscible in their liquid state but completely immiscible as solids, i.e, the solid phases that form consists of pure components.

The phase diagram for **salol-thymol system** is shown on the next slide showing four regions, i.e., region containing:

- Single liquid phase
- Solid salol & a conjugate liquid phase
- Solid thymol in equilibrium with a conjugate liquid phase
- Both components as pure solid phases

Note: Except the first region, other regions are comparable to 2 phase region of the phenol- water system.

It is possible to compute to calculate both composition & relative amount of each phase from the knowledge of the tie lines & phase boundaries



Phase diagram for the thymol- salol system showing eutectic point

- As shown above, if in a system containing 60% by weight of thymol in salol temperature is raised to 50 ^{o}C, & then gradually cooled, the following sequence of phase changes can be observed.
- The system remains as a single liquid until the temp. falls to 29 ^{o}C, at w/h minute amount of solid thymol separates form a two-phase solid-liquid system
- At 25 ^{o}C, system x (from x_1 to x_4) is composed of liquid phase, a_1 with composition 53% thymol in salol) & pure solid thymol b_1. The weight ratio of a_1 to b_1 = 100-60/60-53 = 40/7, hence a_1:b_1 = 5.7: 1

- When temp. is reduced to 20 °C, [pt x_2] composition of liquid phase is a_2 (45% by weight of thymol in salol), while the solid phase is still pure thymol, b_2. The phase ratio, $a_2 : b_2$ = (100-60)/ (60-45) = 40/15 =2.67:1
- At 15 °C (pt x_3), composition of liquid phase is 37% thymol in salol (a_3). The weight ratio of liquid phase to pure solid thymol(a_3:b_3)=(100-60)/ (60-37) =40/23 = 1.74:1
- Below 13 °C, the liquid phase disappears all together & the system contains two solid phase of pure thymol & pure salol
- At 10 oC (pt x_4), the system contains an equilibrium mixture of pure solid salol(a_4) & pure solid thymol(b_4) in a weight ratio of (100-60)/(60-0) = 40/60 = 0.67: 1

Note:

- As system x is progressively cooled, the result indicate that more & more of thymol separates as solid
- A similar sequence of phase changes is observed if system y is cooled in a like manner where by solid salol phase is separated at 22 °C
- At 13 °C, a liquid phase exist in the salol-thymol system . This point on the phase diagram is called eutectic point, containing 34% thymol in salol. The three phases that coexist at eutectic point are solid thymol, liquid salol and solid salol phases. The eutectic point which denotes invariant system has F = 0

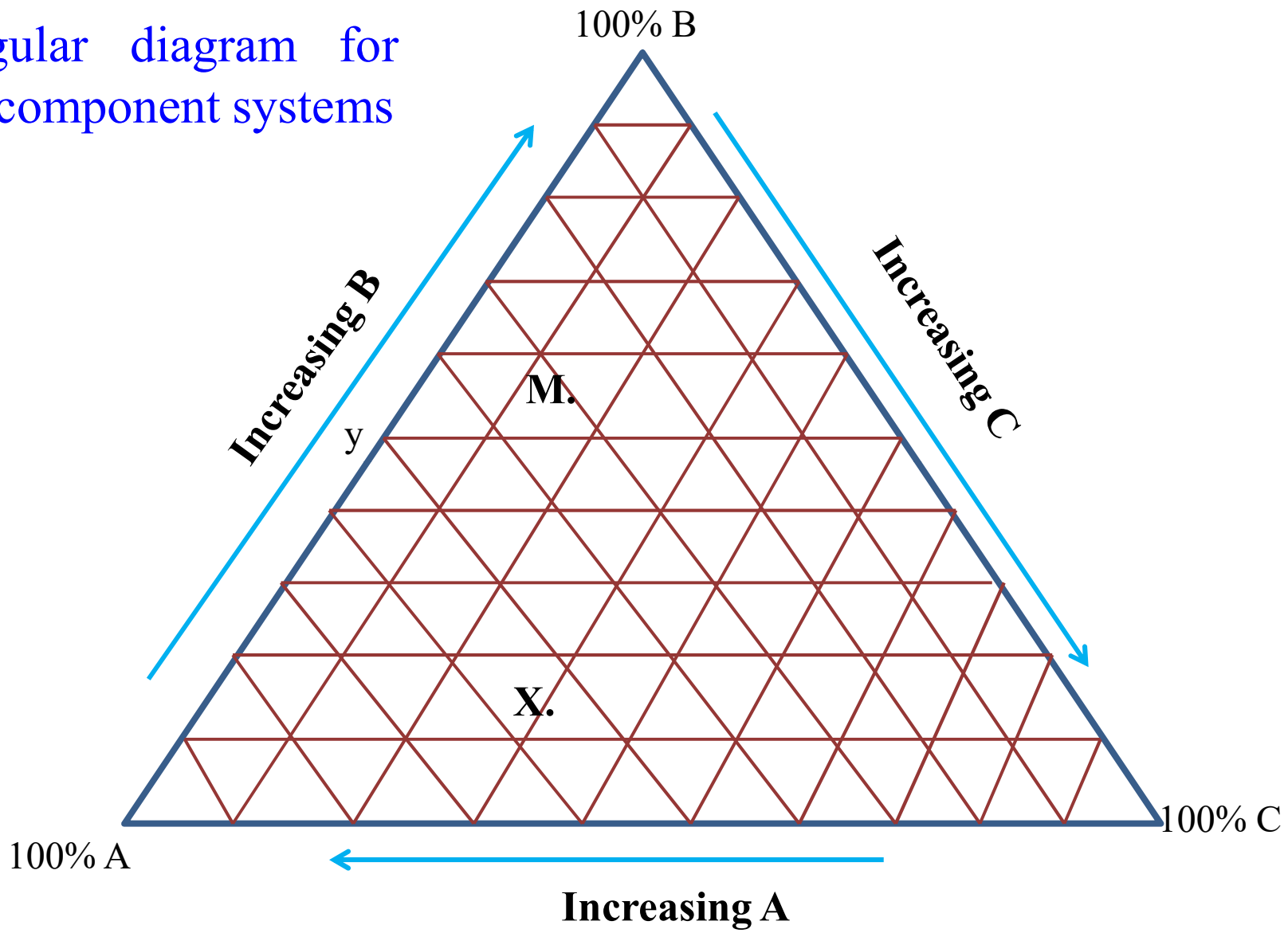
Phase equilibria of three-component systems

- In a ternary system having only one phase, F= 3-1+2 =4, for a noncondensed system
- The four degrees of freedom are temp., pressure & concentrations of two of the three components
- Only 2 concentration terms are required since the sum of these subtracted from the total will give concentration of the third component
- If the system is considered as condensed system & temp. is hold constant, then F= 2. Thus, planar diagram can be used to disclose phase diagram.
- However, using triangular coordinate graph paper is more convenient to illustrate ternary systems
- Conc. in a ternary systems is expressed on a weight basis

Rules relating to Triangular Diagrams

- Each of the three corners or apex represent 100% by weight of one component(A, B or C). Thus, apex of a triangle represent 0% of the other two components
- The three lines joining the corner points represent two-component mixtures of the three possible combination of A, B or C. Thus, the lines AB, BC &CA are used for two-component mixtures of A &**B, B & C** and **C & A,** respectively.
- Divide each line into 100 equal units so that any location on the line is related to % concentration by weight of each components on the respective line
- The area within the triangle represents % by weight of all the three components namely Component A, B & C

Triangular diagram for three-component systems



Example: What is the percent composition of the ternary systems at point X?

Solution

- The line parallel to AC that cuts point x is equivalent to 15%, hence at point x the composition of the system contains 15% of B & 85% of A & C together
- Along the line AB, C= 0, as one move from line B towards C across the diagram, conc. of C increases until at the apex, C = 100%
- Point x lies on the line parallel to AB that is equivalent to 30% of C. Therefore, % weight of component A is given by: [100 – (30 + 15)]% = 55%
- Thus the percent compositions of the ternary systems at point X are 55% of A, 15% of B & 30% of C

Application of Phase Diagrams to Pharmaceutical Systems

Phase diagrams were used as:

- Solubilization of two- and three- component pharmaceutical systems
- Formulation of microcapsule, nanocapsule and microemulsion, nanoemulsion, etc
- Stability studies
- Examination of biological activity

Unit 3: Interfacial Phenomena (8 hrs)

3.1. Liquid interface (surface/interfacial tension, measurement of surface/interfacial tension, surface free energy, spreading

3.2. Adsorption at liquid interfaces (surfactants: basic concepts, the HLB system and applications)

3.3. Adsorption at solid interfaces (Solid/gas interface, solid/liquid interface, Adsorption isotherms)

Introduction

- When phases exist together boundary between two of them is called interface
- The properties of the molecules forming interface is different from those molecules in the bulk of each phase, thus they are forming 'interfacial phase'.

  Is it correct in terms of phase rule???? Discuss!
- Phase is a mass of substance (solid, liquid, or gas) that possesses a well-defined boundary
- There are several types of interfaces at the boundaries between any two states of matter (gas, liquid, or solid), which can be gas–liquid, gas–solid and liquid–solid, or at boundaries between two immiscible phases of the same state: liquid–liquid or solid–solid interfaces.
- However, there cannot be gas–gas interface, as two gaseous materials would mix together rather than form an interface

Classification of Interfaces	
Types of Phases	**Examples of Interfaces**
Gas–gas	No interface possible
Gas–liquid [Liquid surface]	Body of water exposed to atmosphere
Gas–solid [Solid surface]	Table top
Liquid–liquid interface	Emulsion
Liquid–solid interface	Suspension
Solid–solid interface	powder particles in contact with each other

Note: Interfacial phenomena are significant factors that affect

- Absorption of drugs onto solid adjacent in dosage forms
- Penetration of molecules through biological membranes
- Emulsion formation & stability
- Dispersion of insoluble particles in liquid to for suspension

Liquid interfaces

A. Surface tension

- It is a net inward force that molecules at the surface exert on molecules in the bulk
- It describes the interface b/n liquids and vapor or gas
- In the bulk of the phase, the binding forces b/n the molecules are equivalent in every direction, while the molecules on the surface are subjected to intermolecular forces in the direction of the interface and toward the bulk
- In the bulk of a phase, a molecule is surrounded by other molecules of the same type and encounters similar forces in all directions, which tend to neutralize each other. At the interface, a molecule encounters directionally different forces (Figure 3.1).
- Forces between molecules of the same type within a phase is cohesion, whereas forces between molecules of different types at the interface is adhesion.

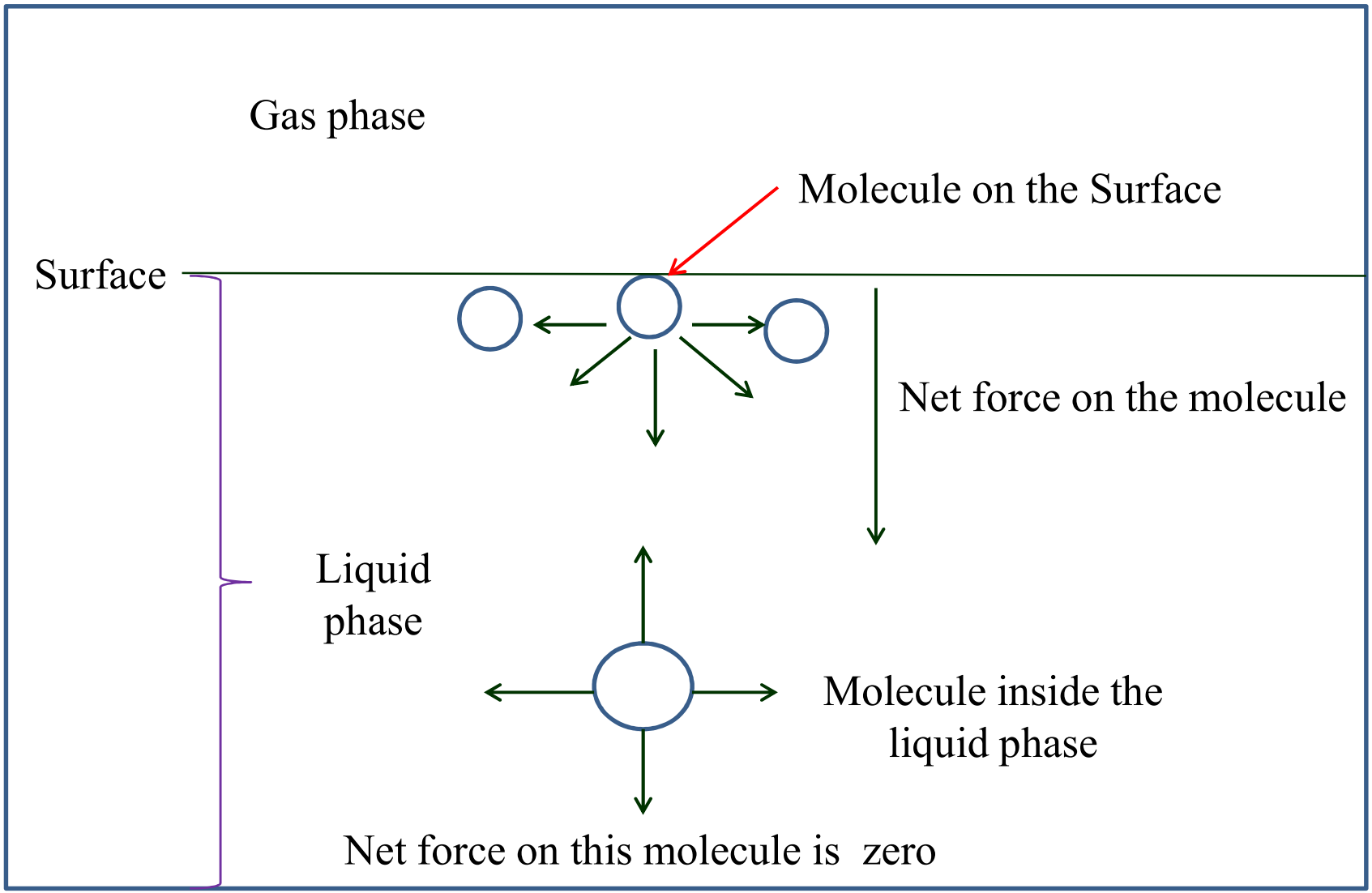
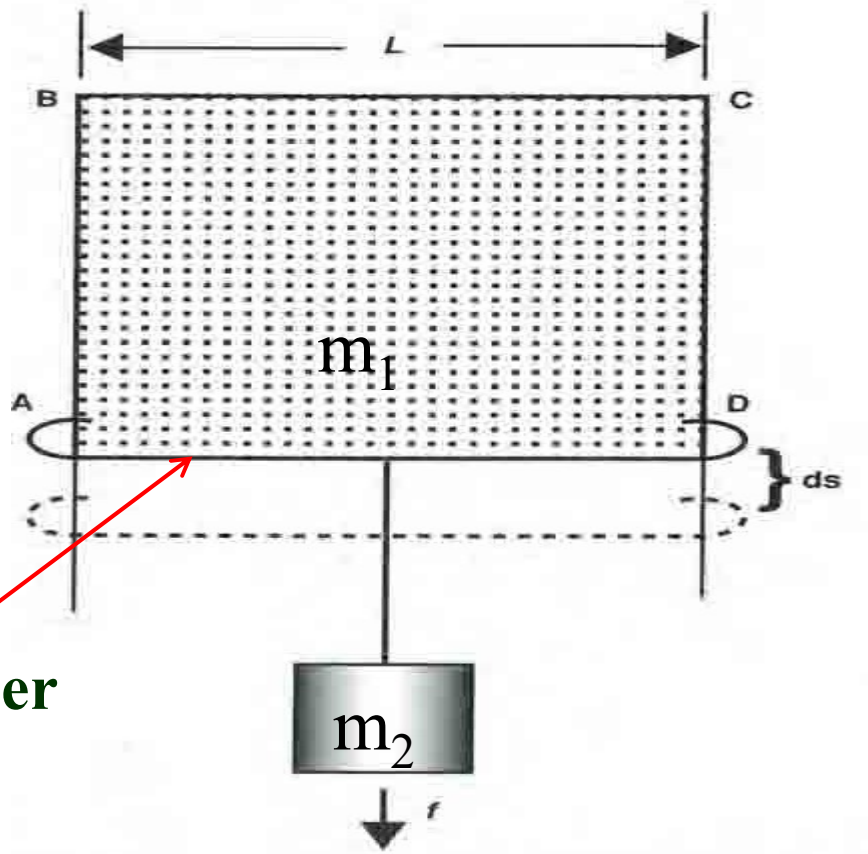


Fig. 3.1:Attraction forces acting on molecules at the surface and in the bulk of the liquid



Wire frame apparatus used to demonstrate the principle

$$\gamma = \frac{(m_1 + m_2)g}{2l} = \frac{F}{2l}$$

Surface tension is the **force per unit length** that must be acting parallel to the surface at right angles to a line of 1m length anywhere in the surface

- If the length of the bar is 5 cm and the mass required to break a liquid film is 0.5 g. What is the surface tension of the soap solution? What is the work required to pull the wire down 1 cm?

  $\gamma = fb/2L = (0.50\ \text{g} \times 981\ \text{cm/s}^2)/10\ \text{cm} = 49\ \text{dyn/cm}$

  $Wa = \gamma\Delta A = 49\ dyn/cm \times 10\ cm2 = 490\ ergs$

Surface free energy

- Surface tension tend to decrease the surface
- If one is to increases the surface (i.e., brings molecules from the bulk of the phase to the surface), work (W) should be done against the forces in the surface[i.e, force of surface tension].
- The surface free energy per unit area, or surface tension, is a measure of this work
- I\t is the minimum amount of work required to bring molecules to the surface from the interior to expand the surface by unit area [**$\Delta A = 2l \times ds$**]:

$$W = \gamma \cdot \Delta A$$

- where *W is the work done (ergs), γ is the surface tension (dyne/cm), and ΔA is the increase in area* (cm^2).

$$W = F.ds/\text{ unit area} = F.ds/2l.ds = F/2l = \gamma$$

Note: Surface tension & surface free energy are dimensionally equivalent & numerically equal

B. Interfacial tension & Interfacial fee energy

i. Interfacial tension

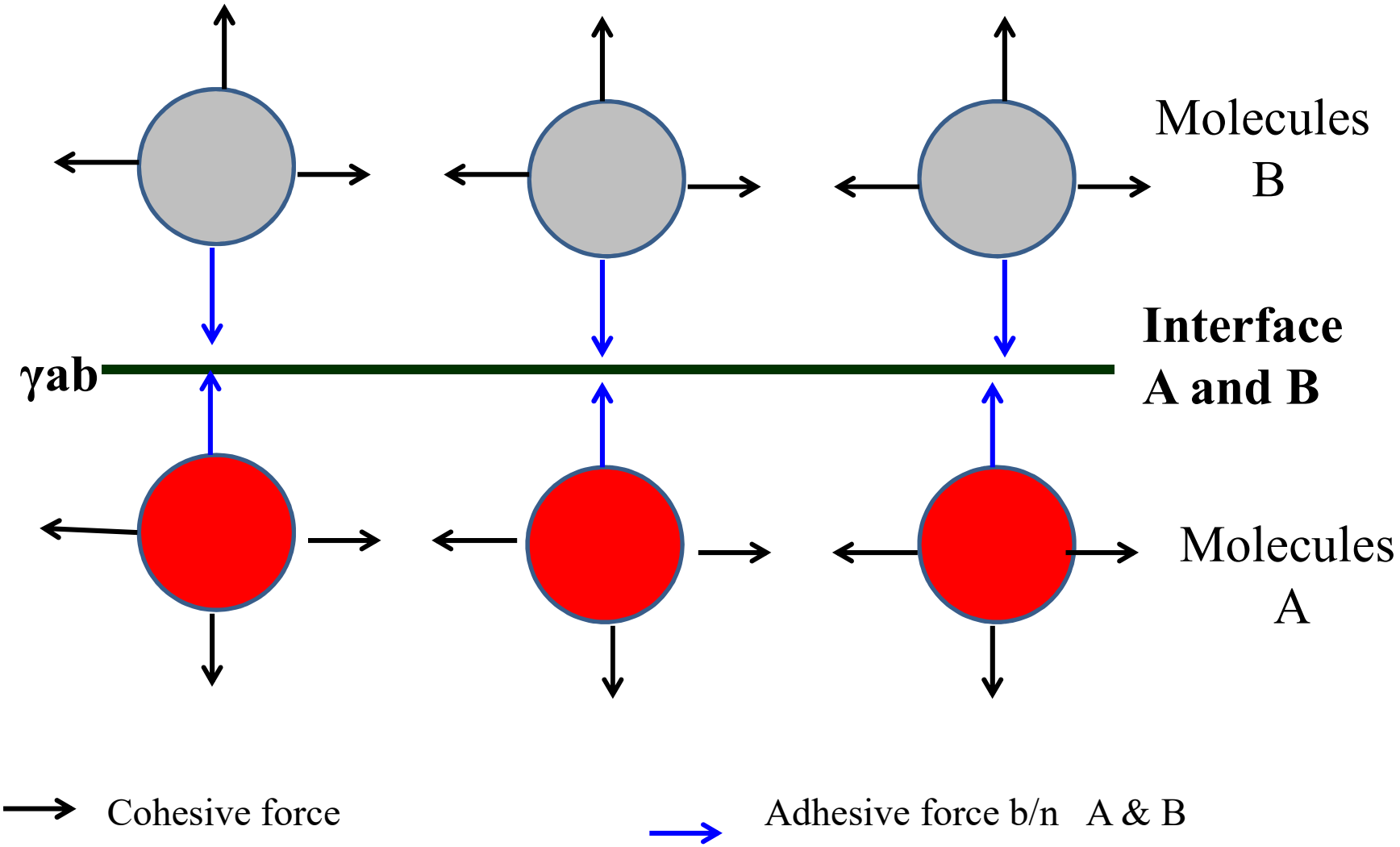
It is the force per unit length (dyne/cm) existing at the interface between two phases other than gas-liquid & gas-solid. The later interfaces have surface tension

Interfacial tensions are less than surface tension if adhesion forces b/n the liquid phases forming an interface is greater than the adhesion forces b/n the liquid- gas interfaces

Note:

- Interfacial tension never exists between liquids that are miscible at all proportions

Schematic representation of intermolecular cohesive forces at an interface



- When the surfaces of liquids A and B are separated from each other, they have their own surface tensions, γa and γb.
- When the two surfaces come into contact with each other to form an interface, an attractive force between molecules of A and B appears
- This attractive force partially compensates for the excess energy of the molecules present at the surface of A and B and consequently reduces the surface tension of two liquids
- In term of work done with the newly created interface between liquids A and B,

  $Wa = \gamma a + \gamma b - \gamma ab$, where Wa is the adhesion work done (ergs), γa and γb are the surface tension of liquid A and B, respectively (dynes/centimeters), and γab is the interfacial tension of A and B (dynes/centimeters).

ii. Interfacial free energy

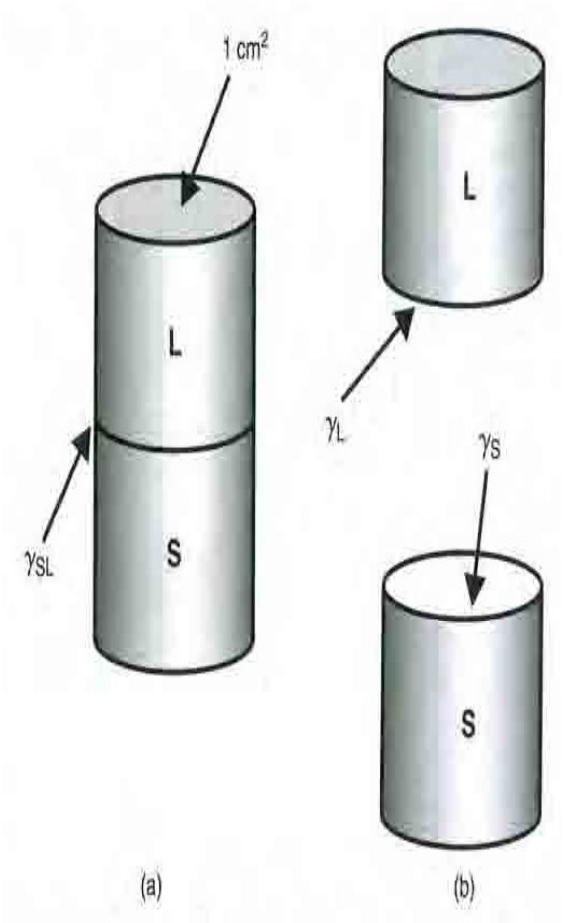
It is the work done to increase the surface area [A] at the interface

$$W = \gamma \Delta A \text{ , where}$$

W = work done expressed in ergs

γ = Surface tension in dyne/cm

ΔA= Increase or change in surface area



Representation of work of adhesion involved in separating a substrate & an overlying liquid

Spreading coefficient

- When liquid 'L' such as oleic acid is placed on the surface of sublayer liquid such as water, it will spread as a film if the force of adhesion b/n liquid 'L' molecules & liquid 'S' molecules is greater than the cohesive force b/n liquid 'L' molecules themselves
- Work of adhesion is the energy required to break attraction b/n unlike molecules, as shown by figure 'a'.
- Figure 'a' shows a hypothetical cylinder [1cm^2) of the sublayer liquid, S, overlaid with a similar section of spreading liquid, L.

- The work required to separate the two sections of liquids is given by: $\mathbf{W = \gamma \Delta A}$
- Figure 'b' shows that the work done is equal to the newly created surface tensions, γ_L & γ_S, minus the interfacial tension, γ_{LS} , that has been destroyed in the process. The work of adhesion (W_a) is given by : $\mathbf{W_a = \gamma_L + \gamma_S - \gamma_{LS}}$
- Work of cohesion is required to separate molecules of spreading liquid so that it can flow over the sublayer, as shown below.
- Obviously, no interfacial tension exists between the like molecules of the liquid. When the hypothetical 1 cm^2 cylinder is divided into two new surfaces, each with a surface tension of γL is created. Thus, work of cohesion is given by: $\mathbf{W_c = 2\gamma_L}$

Spreading Coefficient [S]: is a concept used to assess ability of one liquid to spread over another liquid

Assume that oil is to spread over water surface

The oil will spread over water surface if the work of adhesion b/n the oil molecules & water molecules is greater than the cohesive force b/n the oil molecules themselves

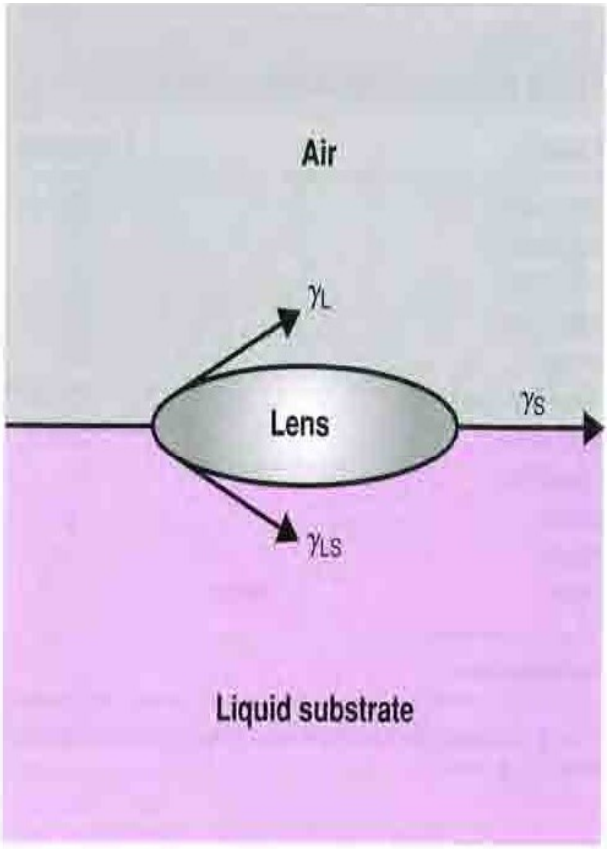
$S = W_a - W_c$

$= \gamma_L + \gamma_S - \gamma_{LS} - 2\gamma_L$

$= \gamma_S - [\gamma_{LS} + \gamma_L]$

Note: Spreading occurs when value of S is zero or positive, at equilibrium otherwise the liquid expected to spread forms a lens and S has a value of negative.

Spreading coefficient with negative value



Forces existing at a surface of a lens floating in a substrate liquid

Before final equilibrium is attained, S value can be positive, as the liquid spread over the substrate liquid

However, mutual saturation occurs when final equilibrium is maintained so that the final Spreading coefficient will have negative value due to coalescence of excess liquid into a lens

Note: Reversal in value of S occurs due to reduction in value of γ_S but not in value of γ_{LS} since interfacial tension occurred under conditions of mutual saturation

Example

If surface tension of water, γ_s is 72.8 dynes/cm at 20 ^{0}C, the surface tension of benzene, γ_l , is 28.9 dynes/cm and interfacial tension b/n benzene & water, γ_{ls}, is 35 dynes/cm. Following equilibrium, γ_s, is found to be 62.2 dynes/cm and γ_l is 28.8 dynes/cm.

Required

1. Initial spreading coefficient 2. Final spreading coefficient

Solution

1. Initial spreading coefficient = $\gamma_S - [\gamma_{LS} + \gamma_L]$

$= 72.8 - (28.9 + 35) = 8.9$ dynes/cm or 8.9 erg/cm

2. Final spreading coefficient = $\gamma_{S'} - [\gamma_{LS} + \gamma_{L'}]$

$= 62.2 - [35 + 28.8] = -1.6$ dynes/cm

Note:

Although benzene spreads initially on water, at final equilibrium there is formed a saturated monolayer with the excess benzene (saturated with water) forming a lens

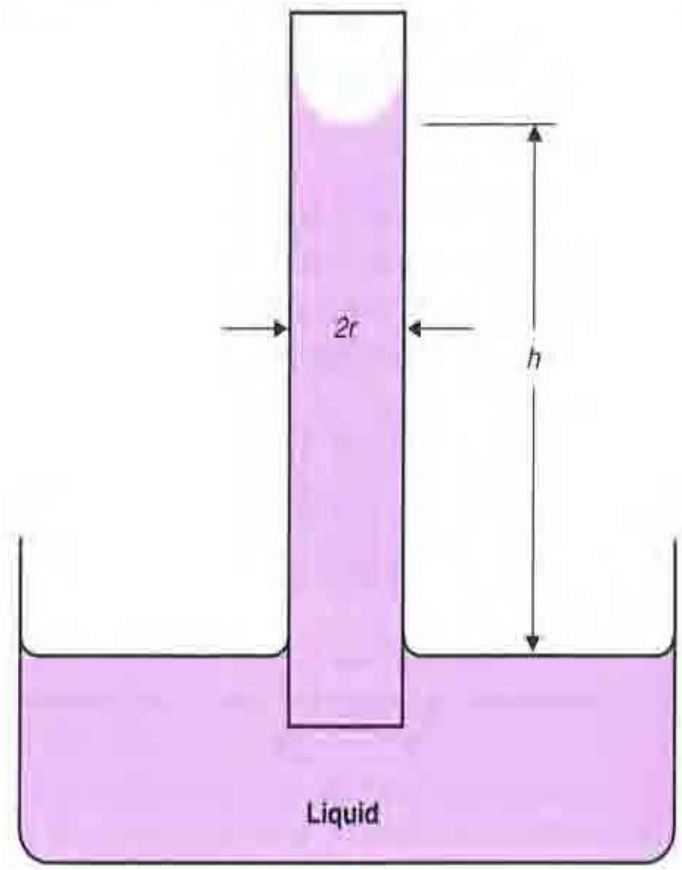
Note:

- As the carbon chain of organic acid increases, the ratio of polar-nonpolar character decreases & the spreading coefficient on water decreases.
- Many nonpolar substances, such as liquid petrolatum (S= -13.4) fail to spread on water.
- Benzene spreads initially on water not because it is polar but because the cohesive forces b/n its molecules are much weaker than the adhesion for water
- Application of spreading coefficients relates surface of skin with applied pharmaceutical preparation. Surface of skin is bathed in aqueous-oily layer having polar-nonpolar character similar to that of a mixture of fatty acids. For a lotion with a mineral oil base to spread freely & evenly on skin, its polarity & hence its spreading coefficient should be increased by adding surfactants

Measurement of surface tension & interfacial tension

- Several methods are in use to measure surface tension & interfacial tension but the most commonly employed are:
  - ❖ Capillary rise method
  - ❖ Tensiometer method

A. Capillary rise method: Used to measure surface tension but not interfacial tension



When a capillary tube is placed in a liquid contained in a beaker, the liquid generally rises up the tube a certain distance. Because the force of adhesion between the liquid molecules and the capillary wall is greater than the cohesion between the liquid molecules, the liquid is said to *wet* the capillary wall, spreading over it and rising in the tube

Because of the surface tension, the liquid continues to rise in the tube, but because of the weight of the liquid, the upward movement is just balanced by the downward force of gravity.

The upward vertical component of the force resulting from the surface tension of the liquid at any point on the circumference is given by

$$a = y\cos(\theta)$$

- Total upward force around inside circumference of the tube is given by: **$2\pi r\gamma\cos\Theta$**

  Note: For water & other commonly used liquids, Θ is insignificant, as the liquid wets the capillary, thus for practical purpose it is taken as zero.

  Accordingly, $2\pi r\gamma\cos\Theta$ is reduced to $2\pi r\gamma$

  where

  - Θ is contact angle b/n liquid surface & capillary wall,
  - $2\pi r$ is inside circumference of the capillary

- The counteracting force of gravity[mg] is given by the product of cross-sectional area, πr^2, the height, h, of the liquid column to the lowest point of the meniscus, the difference in the density of the liquid,ρ & its vapor density ,ρ_o, & acceleration of gravity:**$\pi r^2 h\rho g$**
- When, liquid has risen to its maximum height, which can be read from the calibrations on the capillary tube, the opposing forces are in equilibrium, hence surface tension can be computed from the following r/ship:

$$2\pi r\gamma = \pi r^2 h\rho g$$

$$\gamma = \underline{rh\rho g/2}$$

Example: Calculate surface tension of Chloroform using Capillary rise method if sample of chloroform rose to a height of 3.67 cm at 20 ^{o}C in a capillary tube having inside radius of 0.01 cm & density of chloroform is 1.476 g/cm^3.

Solution

Givens: h=3.67cm, ρ=1.476g/cm^3, r=0.01cm,

g = 981cm/sec^2

γ = rhρg/2

= [0.01cm x 3.67 cm x 1.476 g/cm^3 x 981cm/sec^2]/2

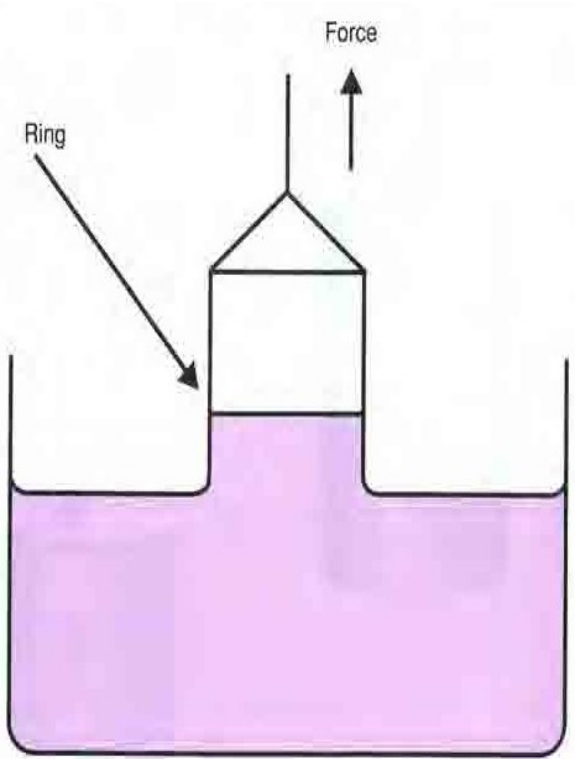
= 26.6 g/sec^2 = 26.6 g.[cm/sec^2]cm= 26.6 dynes/cm

Exercise

1. Calculate surface tension of a 2% w/v solution of a wetting agent that has a density of 1.008 g/cm3 and that rises 6.60 cm in a capillary tube having an inside radius of 0.02 cm.
2. Surface tension of an organic liquid is 25 ergs/cm^2, surface tension of water is 72.8 ergs/cm^2, & interfacial tension between the two liquids is 30 ergs/cm^2 at 20°C.

   What is the work of cohesion of the organic liquid and the work of adhesion between the liquid and water at 20°C?

B. Du Nuoy Tensiometer [or Ring method]



Du Nuoy Tensiometer

- Used for measuring surface tension & interfacial tension
- **Principle of the instrument:** The force necessary to detach a platinum-iridium ring immersed at the surface or interfaces is proportional to the surface tension or interfacial tension.
- The force required to detach the ring in this manner is provided by a torsion wire & is recorded in dynes on a calibrated dial
- In effect, the instrument measures the weight of liquid pulled out of the plane of the interface immediately before the ring becomes detached

$$\gamma = \frac{\text{Dial reading in dynes x Correction factor}}{2 \text{ x RingCircumference}} \quad \text{Or} \quad \gamma = \frac{m.g.\beta}{4\pi r}$$

Example

If the mass of the liquid lifted by the ring with radius 0.8078 cm is 0.7866 g and correction factor is 0.9617, then find the tension responsible to counteract the up lifting force at equilibrium

Solution

Givens: r = 0.8078 cm, m= 0.7866 gm, β = 0.9617

$$\gamma = \frac{m.g.\beta}{4\pi r}$$

= [0.7866 gm x981 cm/s^2 x 0.9617]/ 4 x 0.8078 cm π

= 73.14 dynes/cm or 73.14 ergs/cm^2

Adsorption at liquid interfaces[liquid–liquid and liquid–gas interface]

- At the liquid–gas interface, cohesive forces are generally greater than adhesive forces, leading to an inward pull on the molecules toward the bulk. This force pulls and keeps the molecules of the interface together and tends to contract the surface, resulting in minimization of the exposed surface area.
- Expansion of surface requires application of a force called surface tension at **liquid–gas interface** or interfacial tension at **liquid–liquid interface**

- When certain molecules or ions are dispersed in the liquid, they move of their own accord to the interface. Their higher concentration in the interface exceeds their concentration in the bulk. Such phenomenon, where the added molecules are partitioned in favor of the interface is termed adsorption [positive adsorption]
- Occurrence of positive adsorption automatically reduces both surface/interfacial tension and surface/interfacial free energy of the system
- Other materials such as organic ions are adsorbed in favor of the bulk, leading to a negative adsorption & a corresponding increase in surface/interface tension & surface/interface free energy

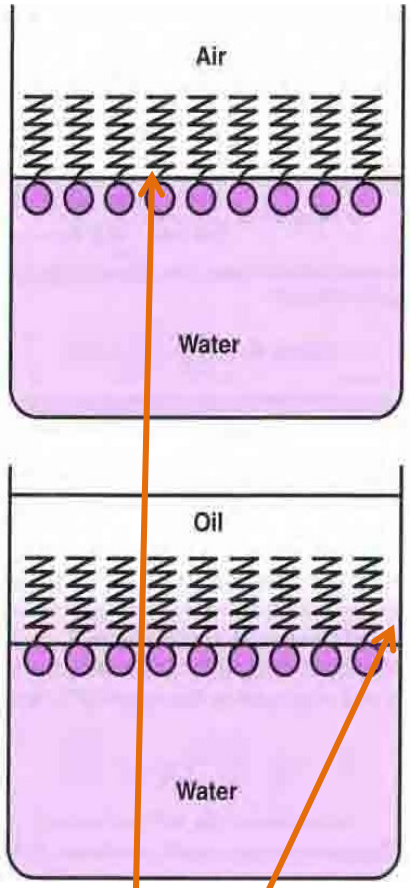
Adsorption vs absorption??

Surfactants: Basic concepts, HLB system & applications

Surfactants: Basic concepts

- Molecules & ions that are adsorbed at interfaces are termed SAA/surfactants or Amphiphiles
- Amphiphile is molecule or ion that has a certain affinity for both polar & nonpolar solvents
- Depending on the number & nature of the polar & nonpolar groups present, amphiphile may be predominantly hydrophilic, lipophilic or reasonably well balanced b/n these two extremes
- Straight-chain alcohols, amines & acids are amphiphiles that change from being predominantly hydrophilic to lipophilic as the № of carbon atoms in the alkyl chain increased.
- Thus, ethyl alcohol is miscible with water in all proportions, aqueous solubility of amyl alcohol, $C_5H_{11}OH$ is much reduced whereas acetyl alcohol, $C_{15}H_{33}OH$ is strongly lipophilic & insoluble in water

- It is the amphiphilic nature of SAAs that causes them to adsorb at the interfaces [L/G or L/L interfaces]
- Thus, in aqueous dispersion of amyl alcohol, the polar alcoholic group is able to associate with the water molecules. The nonpolar portion is rejected, however, b/c the adhesive forces it can develop with water are small in comparison to the cohesive forces b/n adjacent water molecules, the amphiphile is adsorbed at the interface



Adsorption of fatty acid molecules at water-air interface & water-oil interface

- For amphiphile to be concentrated at the interface, it must be balanced with the proper amount of water-soluble & oil soluble groups

Reason:

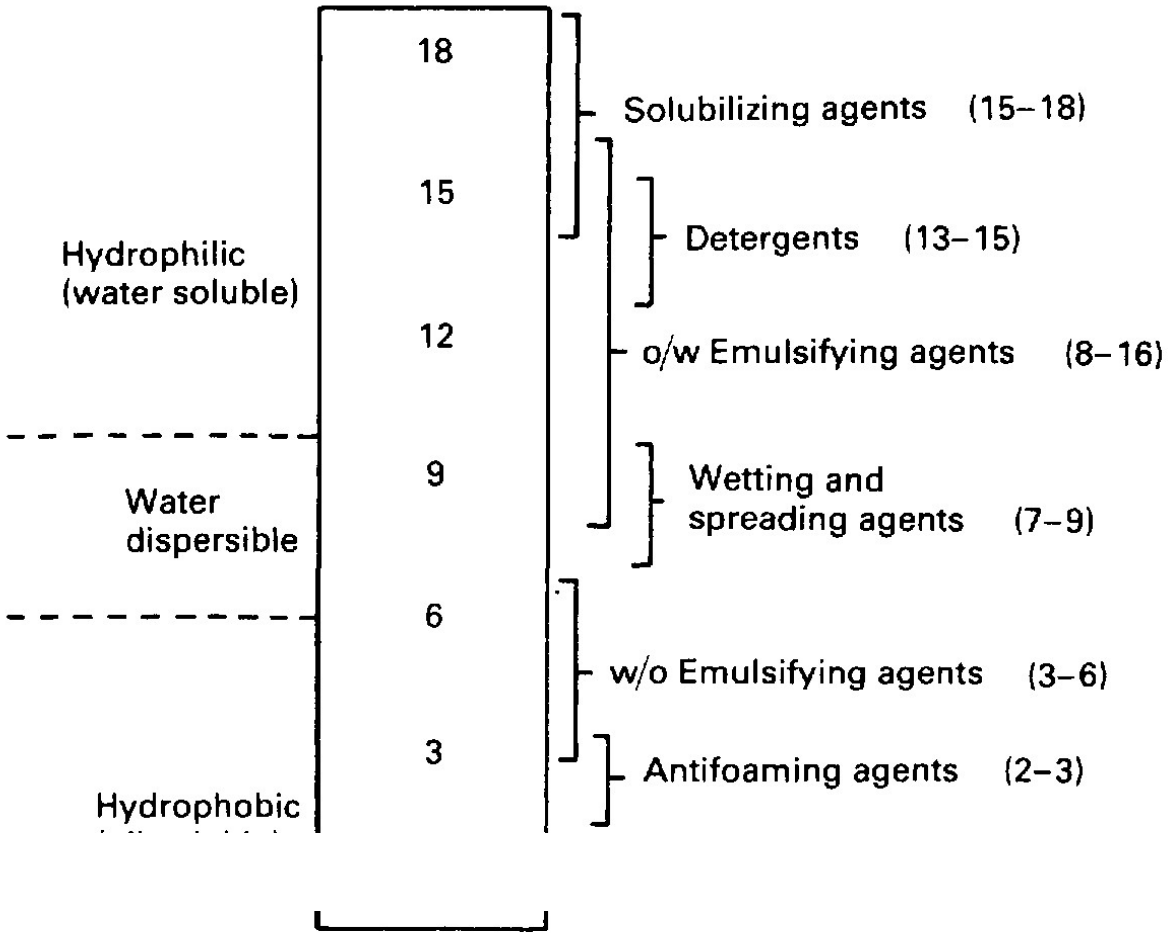
If the molecule is too hydrophilic, it remains within the body of the aqueous phase & exerts no effect at the interface. Likewise, if it is too lipophilic, it dissolves completely in the oil phase & little at the interface

Systems of Hydrophile-Lipophile balance[HLB]

- Griffin devised an arbitrary scale of values [number system] as a measure of hydrophilic-lipophilic balance of SAAs
- The higher the HLB value of an agent, the more hydrophilic it is.
- Tweens, polyoxyethylene derivatives of the span are hydrophilic with HLB value 9.6 to 16.7
- Spans, sorbitan esters derivatives are lipophilic with HLB value 1.8 to 8.6
- HLB of nonionic SAA whose only hydrophilic portion is polyoxyethylene is calculated using the formula:

  HLB= E/5, where E is % by weight of ethylene oxide
- HLB of SAA with a № of poyhydric alcohol fatty acid esters, such as glyceryl monoestrate can be estimated by: **HLB = 20(1- S/A)**, where S is saponification № of the ester & A is the acid № of the fatty acid

Classification of surface active agents based on HLB scale



HLB scale showing classification of surfactant function.

Example:

1. Find HLB of polyoxyethylene sorbitan monostrate [Tween 20] for which S=45.5 & A is 276.

Solution:

$$HLB = 20[1-S/A] = 20[1- 45.5/276]= 16.7$$

- The desired HLB numbers can also be achieved by mixing lipophilic and hydrophilic surfactants.
- Overall HLB value of the mixture is calculated as the sum of the fraction multiplied by the individual HLB

2. In a mixture of 30% Span 80 (HLB = 4.3) and 70% Tween 80 (HLB = 15) what is the overall HLB value?

Solution

$$HLB = (0.3 \times 4.3) + (0.7 \times 15) = 11.8$$

Exercise:

How many grams of Span 80 (HLB 4.3) and Tween 80 (HLB 15) must be mixed to make 30 g of surfactant mixture with an HLB of 12.0?

[Answers: 8.4 g of Span 80 and 21.6 g of Tween 80]

Adsorption at solid interfaces

- **Adsorption** refers to surface binding of a liquid or gas molecule (*adsorbate) onto a solid surface (adsorbent).*
- *Examples of adsorbents are highly porous solids, such as charcoal, silica gel, and finely divided powders such as talc.*
- *Adsorbate could be any molecule, such as drug compound.*
- Adsorption of material at solid interfaces can take place from either an adjacent liquid or gas phase
  - Adsorption at Solid/gas interface
  - Adsorption at solid/liquid interface
  - Adsorption isotherms

- The study of adsorption of gas arises in removal of objectionable odors from rooms & food, operation of gas masks & measurement of dimensions of particles in powder
- The principles of solid /liquid gas adsorption is used in decolorizing solutions, adsorption chromatography, detergency & wetting .

Solid/gas interface

Degree of adsorption of a gas onto solid depends on:

- Chemical nature of adsorbent[materials used to adsorb gas] & adsorbate[substances being adsorbed]
- Surface area of the adsorbent
- Temperature of adsorbed gas
- partial pressure /concentration of adsorbed gas

Types of adsorption:

1. Physical adsorption

- Associated with van der Waals forces
- It is nonspecific reversible
- Adsorbed gas can be desorbed from adsorbent [solid] by increasing temperature & reducing pressure

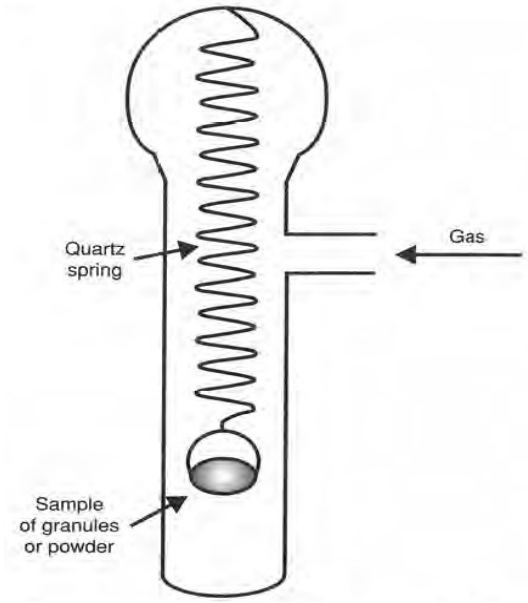
2. Chemical adsorption [chemisorption]

❖ Adsorbate is attached to adsorbent primarily by chemical bonds such as covalent bonds

- Chemisorption is specific, irreversible, forms monolayer of adsorbed substances and may require activation energy as the process is slow

Adsorption isotherm is the relationship b/n amount of gas physically adsorbed onto a solid at equilibrium pressure or concentration at constant temperature[hence the term: **isotherm]**

The № of moles, grams or millilitres, x, of gas adsorbed on 'm' grams of adsorbent at standard temperature & pressure is plotted on vertical axis against the equilibrium pressure of the gas in mm Hg on the horizontal axis



Apparatus used to measure adsorption of gas on solid

Freundlich isotherm equation &graph

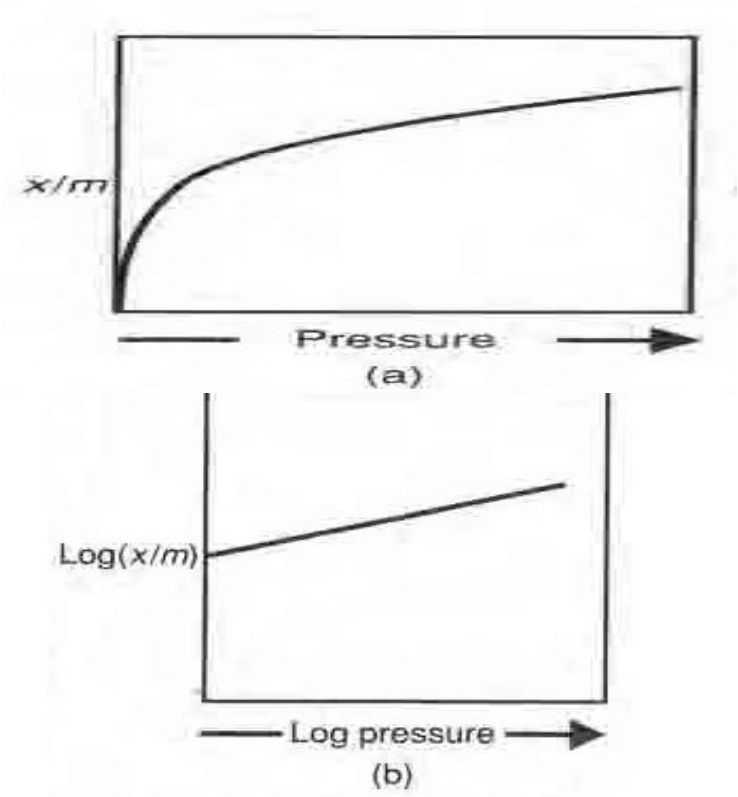
Exponential form of the equation

$$y = \frac{x}{m} = kp^{\frac{1}{n}}$$

Where y is mass of gas, x, adsorbed per unit mass, m, of adsorbent & k and n are constants that can be evaluated from results of the experiment

Logarithmic form of the equation

$$\log \frac{x}{m} = \log k + \frac{1}{n} \log p$$



Adsorption isotherms for a gas on a solid

(a)Amount ,x, of gas adsorbed per unit mass, m, of adsorbent plotted against the equilibrium pressure.

(b) Log of the amount of gas adsorbed per unit mass of adsorbent plotted against the log of the pressure

y_m

Solid/liquid interface

Many pharmaceutical systems deal with adsorption of solutes from solutions onto solid surfaces

Example:

Adsorption of drug or hydrophilic polymer on suspended drug particles in a suspension or adsorption of drug on activated charcoal administered in the case of oral drug overdose

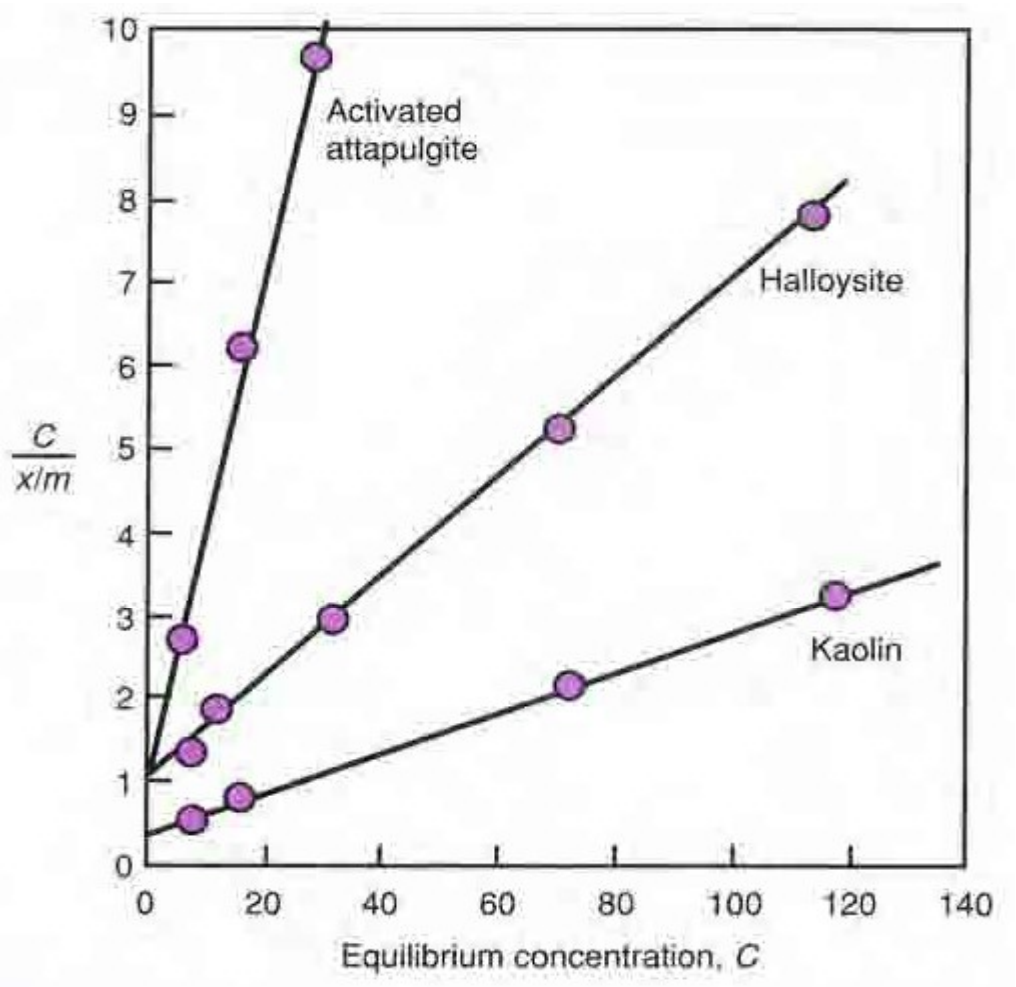
Adsorption of solute molecules from solution can be treated in a manner analogous to adsorption of molecules at solid-gas interface

Langmuir equation: $$\frac{c}{y} = \frac{1}{by_m} + \frac{c}{y_m}$$

Where , C is equilibrium concentration of solute per 100 ml of solution , y is amount of solute, x in mg adsorbed per gram, m, of adsorbent [i.e., y= x/m] and b & y_m are constants

- Adsorption of diphtheria toxin & several bacteria was investigated using different types of clays
- It was concluded that attapulgite, a hydrous magnesium aluminum silicate, was superior to kaolin as intestinal adsorbent
- The results of adsorption of Strychnine on activated attapalgite, halloysite & kaolin , all washed with gastric juice are presented on the graph

Note: The smaller the slope, the better is the adsorption



Adsorption of strychnine on various clays

Biological and pharmaceutical applications of SAAs

1. Compounding stable pharmaceuticals by acting as wetting, foaming, antifoaming & Solubilizing agent
2. Enhancing physical stability of biphasic dosage forms such as suspensions and emulsions by stabilization of solid–liquid & liquid–liquid interface, respectively
3. Improving dissolution rate of poorly soluble drugs by adsorption of small amount of surfactants on surface of drug particles
4. Facilitate drug absorption via membrane by affecting microbial membrane integrity

Example: Ionic SAA such as Quaternary ammonium compounds which have antibacterial action

5) **Facilitating gas exchange in the lungs**.

Biological surfactants in the lungs [**Phosphatidylcholine]** lowers surface tension of alveolar membrane almost to zero. Thus, alveoli can expand easily during inspiration and do not collapse at the end of expiration. If there is little or no surfactant in the lungs to assist these processes, the alveoli collapse, leading to respiratory distress syndrome

6) **Preventing absorption after oral overdose and poisoning** Activated charcoal, magnesium oxide, and tannic acid are administered to reduce absorption of an oral overdose of many drugs such as colchicines, phenytoin, aspirin, and chlorphenamine.

Unit 4: Solubility & Distribution Phenomena (9 hrs)

4.1. Terminologies (solute, solvent, solution, solubility)

4.2. Solute-solvent interactions (polar, nonpolar and semipolar solvents)

4.3. Solubility expressions

4.4. Solubility of gases in liquids

4.5. Solubility of liquids in liquids

4.6. Solubility of solids in liquids

4.7. Distribution phenomena

What is solubility?

- It is amount of substance that dissolves to form a saturated solution at equilibrium at constant temperature and pressure
- It is an intrinsic material property that can be altered only by chemical modification of the molecule

What is Dissolution?

- Dissolution is an extrinsic material property that can be influenced by various chemical, physical or crystallographic means such as complexation, particle size reduction, surface properties, solid –state modification or solubilization enhancing formulation strategies

Solubility expression

The USP describes solubility of drug at fixed temp. & pressure as :

- part of solvent required for one part of solute or
- volume of solvent in which 1 g of solute is dissolved

Example:

1 g of boric acid dissolves in 18 ml of water, or in 4 ml of glycerine at fixed temp. & pressure

- Solubility is also quantitatively expressed in terms of molality, molarity and percentage

Determination of solubility of a solid in a liquid

The following points should be observed in all solubility determinations:

1. The solvent and the solute must be pure
2. A saturated solution must be obtained before any solution is removed for analysis
3. The method of separating a sample of saturated solution from undissolved solute must be satisfactory[filtration at equilibrium temp. of saturated solution]
4. The method of analysing the solution must be reliable [UV spectrophotometer, Chromatography, Volumetric analysis methods]
5. Temperature must be adequately controlled [20 ^{o}C]

Terms of Solubility (USP)	
Terms	**Parts of Solvent Required to Dissolve One Part of Solute**
Very soluble	Less than 1
Freely soluble	[1–10)
Soluble	[10–30)
Sparingly soluble	[30–100)
Slightly soluble	[100–1,000)
Very slightly soluble	[1000–10,000)
Practically insoluble	≥10,000

4.2. Solvent- solute interaction

Polar solvents: Dissolve ionic solutes & other polar substances

- Dipole moment [ability of the solute to form hydrogen bonds] and dipole interaction forces affect solubility of solute
- Water is miscible with all proportions of alcohol & dissolves sugars and polyhydroxy compounds

Nonpolar solvents: Cannot dissolve polar and ionic solutes since they cannot reduce attraction forces between such solutes. They cannot form hydrogen bridges with nonelectrolytes. However, they dissolve nonpolar compounds with similar internal pressures via induced dipole interaction.

Semipolar solvents: Act as intermediate solvents causing miscibility of polar and nonpolar liquids

Example:

- Acetone increases solubility of ether in water
- Propylene glycol increases mutual solubility of water & peppermint oil and water and benzyl benzoate

Note

1. The generalized concept 'like dissolves like', i.e. a polar substance will dissolve in a polar solvent and a non-polar substance will dissolve in a non-polar solvent should be treated with caution

Reason:

Possibility of intermolecular **hydrogen-bond formation** between solute and solvent may be more significant than **polarity**

2. The solubility of substances can be qualitatively predicted by considering polarity, dielectric constant, association, solvation, internal pressures, acid-base reaction and other factors
3. Solubility depends on chemical, electrical & structural effects that lead to mutual interactions b/n solute and solvent

4.3. Solubility of gases in liquids

- ❖ Refers to concentration of dissolved gas when it is in equilibrium with some pure gas above the solution
- ❖ It depends primarily on the pressure, temperature, presence of salts and chemical reactions that the gas undergoes with the solvent

Effect of pressure on gas solubility

- Solubility of gas increases as pressure on the gas increases and vice versa.
- Henry's law: $\sigma P = C_2$ where

σ = Solubility coefficient, C_2 is concentration of dissolved gas[g/ml] and P is partial pressure of undissolved gas above the solution

Note

- Henry's law works if molecules are at equilibrium, only
- Henry's law does not work for gases at high pressures (e.g., N2(g) at high pressure becomes very soluble and harmful when in the blood supply)
- Henry's law does not work if there is a chemical reaction b/n solute & solvent

Example:

HCl (g) reacts with water by a dissociation reaction to generate

$$H^{+}{}_{3}O + \text{and } Cl^{-}$$

Effect of temperature on gas solubility

- Solubility of gas decreases as temperature increases since it causes gas expansion

Salting out: Decreases solubility of gas

- Introduction of electrolyte [NaCl] or non-electrolyte [sucrose] causes liberation of gas from solvent. This phenomenon is called salting out.

Effect of chemical reaction on solubility of gas

- Chemical reaction of gaseous solutes with solvent increases their solubility. Thus, HCl, NH_3 & CO_2 are more soluble in water than O_2 due to their interaction with solvent

Note: Existence of chemical reaction b/n gas and solvent show deviation from Henry's law

4.4. Solubility of liquids in liquids

Frequently two or more liquids are mixed together in the preparation of pharmaceutical solutions.

Examples

- Alcohol + water = Hydroalcoholic solution
- Volatile oil + Water = Aromatic waters
- Volatile oil + Alcohol = Spirits and elixirs
- Ether + alcohol = Cosolvent in collodion
- Fixed oils are blended into lotions, sprays, emulsions

Solubility of liquid-liquid systems can be divided into 2 categories according to level of their solubility into one another

1. **Complete miscibility**
2. **Partial miscibility**

Note: Miscibility refers to mutual solubility of the components in the liquid-liquid systems

1. Complete miscibility:

- Components mix at all proportions
- They create no solubility problems to pharmacists

Eg: Alcohol & acetone, Alcohol & glycerin, H_2O & ROH , Benzene & carbon tetrachloride

2. Partial miscibility:

Results in the formation of two liquid layers each containing some of the other liquid in the dissolved state

Eg: Phenol in H_2O, water & ether

Note:

Mutual solubility increases as temperature increases until critical solution temp.[CST] is reached, where the composition become identical forming homogenous or single liquid phase.

Influence of foreign substances on liquid solubility

- Addition of a substance to a binary liquid system produces a ternary system[3 component system]
- If the added component is soluble only in one of the liquid component, mutual solubility of the binary system decreases.
- If the binary mixture has UCS temperature, the temperature is raised; if it has a lower consolute temperature, temperature is lowered.

Example:

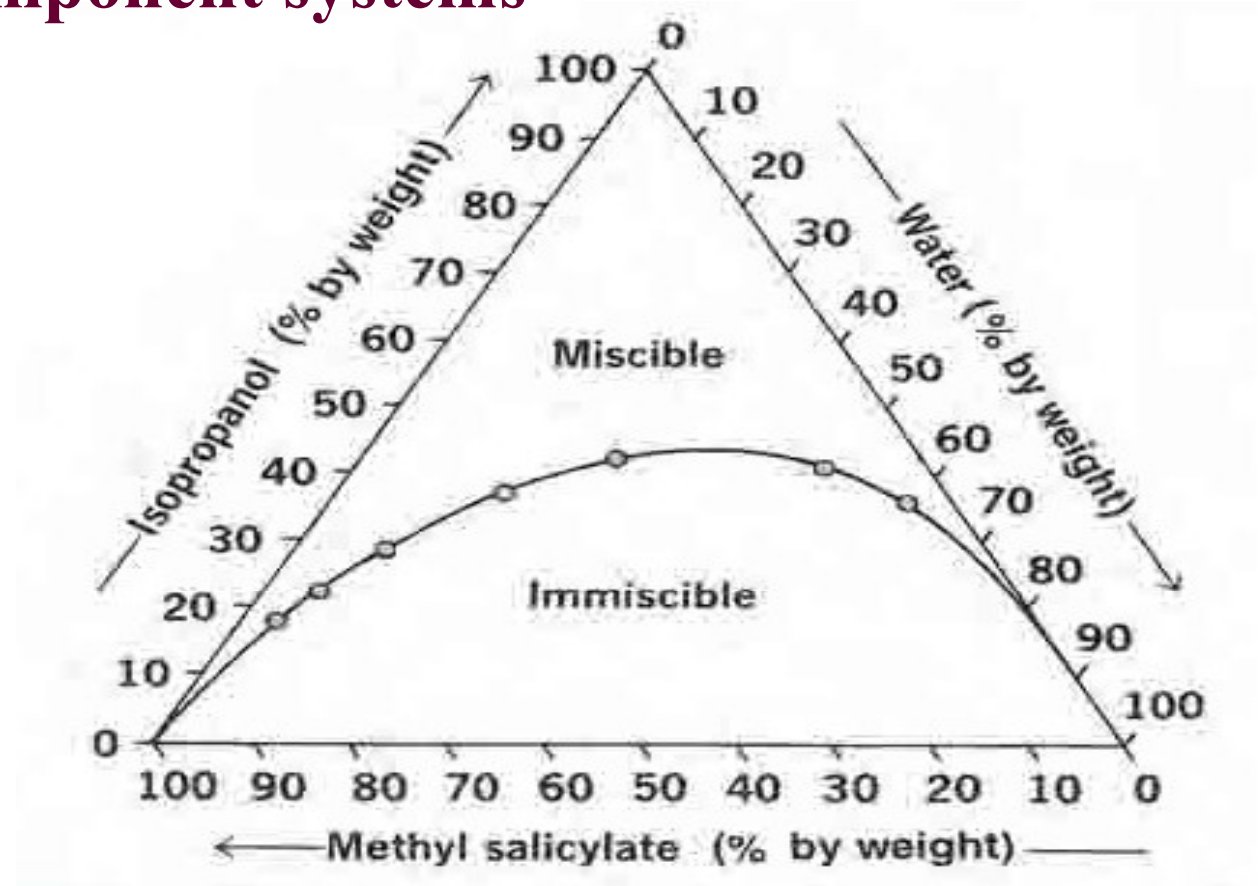
Addition of KCl to phenol-water mixture raises UCST by 8 ^{o}C while addition of 0.1 m naphthalene to same mixture raises UCST by 20 ^{o}C.

- When the added substance is soluble in both liquids forming the binary mixture, the mutual solubility of the binary liquid pair is increased; UCST is lowered and LCST is raised.

Example: Addition of succinic acid or sodium oleate to water- phenol system

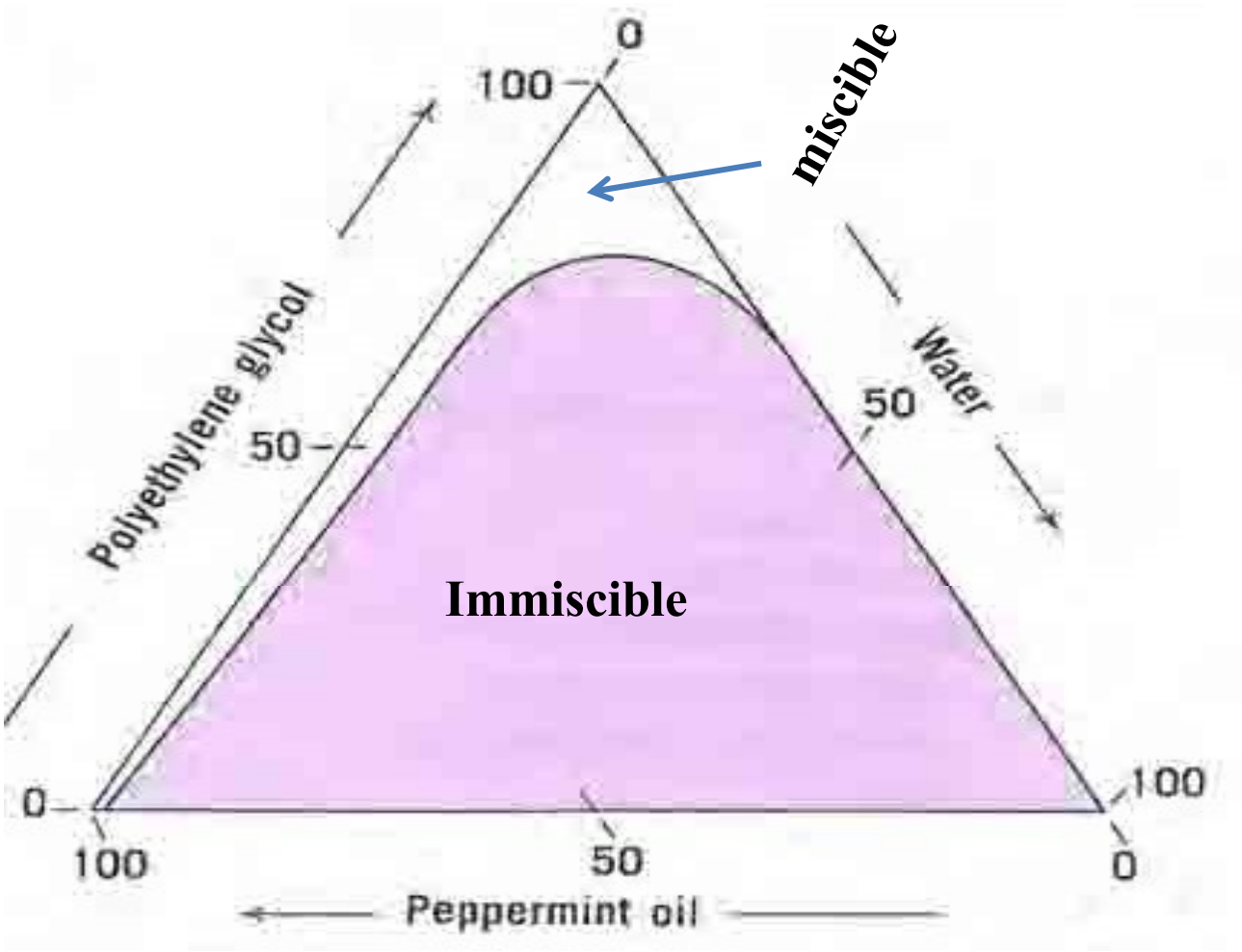
Three component systems

A



Triangular phase diagram for the three component systems:
Methyl salicylate-isopropranol- water

B



A triangular diagram showing solubility of peppermint oil in various proportions of water & Polyethylene glycol

Types of liquid –in-liquid solution

A. Ideal solutions

Ideal solution is a solution that obeys Raoult's law:

$P_i = P_i^o X$ where P_i^o is vapour pressure of pure state;

P_i = partial pressure of the component in the mixture at definite temperature

X = Mole fraction of the component in the solution

B. Real solution: Components in a solution may show negative or positive deviation from Raoult's law

Negative deviation discloses increased solubility due to hydrogen bond formation b/n polar compounds

Positive deviation shows decreased solubility due to association of the molecules of one of the constituents to form double molecules or dimers or polymers of higher order [Formic acid: HCOOH]

Factors affecting solubility of liquids

- Temperature of the system [UCST, LCST]
- Nature of liquid solute & solvent[polar, semiploar, nonpolar]
- Pressure
- Chemical reaction
- Presence of mutually soluble 3rd component

Example: Addition of succinic acid to water- phenol system

4.5. Solubility of solids in liquids : Constituted the most important type of pharmaceutical solutions

- **Ideal solution:** A solution in which heat of solution is equal to heat of fusion & no net heat is released or absorbed during formation of the solution and it is constant & independent of temperature
- Solubility of solid in ideal solution depends on temperature, m.p and molar heat of fusion [ΔH_f] of solid
- Nature of solvent never affect ideal solubility

$$-\log X_2^i = [\Delta H_f (T_o - T)] / 2.303RTT_o$$

X_2^i = ideal solubility of solute[in mole fraction], T_o m.p of solid in Kelvin and **T**= Absolute temperature of solution and R= gas constant= 1.987

Example: What is the solubility of naphthalene at 20^{o}C in an ideal solution? The m.p of naphthalene is 80^{o}C and ΔH_f is 4500cal/mole.

Solution

$$-\log X_2^i = [\Delta H_f (T_0 - T)] / 2.303RTT_o$$

$$= 4500(353 - 293)]/2.303 \times 1.987 \times 353 \times 293$$

$$\log X_2^i = \underline{0.27}$$

$$X_2^i = \underline{0.537}$$

Real solutions [Non-ideal solution] : the activity of a solute in a solution is expressed as the conc. multiplied by the activity coefficient[γ_2]

$$a_2 = X_2 \gamma_2$$

- Converting to logarithms, we have

$$\log a_2 = \log X_2 + \log \gamma_2$$

In an ideal solution, $a_2 = X_2$ and $\gamma_2 = 1$,re=expressing equation of ideal solution in terms of activity we have

$$-\log a_2 = -\log X_2^i = [\Delta H_f (T_0 - T)] / 2.303RTT_o - \log \gamma_2$$

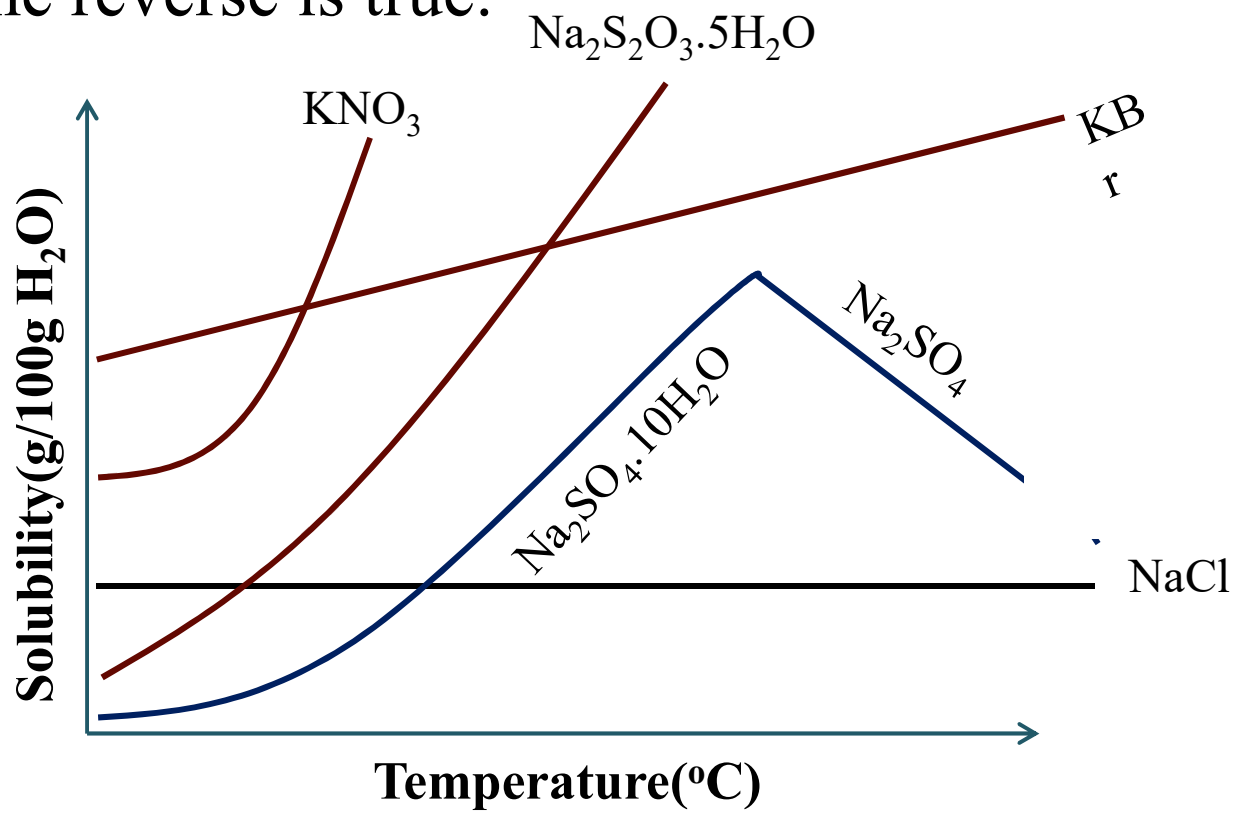
$$-\log a_2 = -\log X_2^i = [\Delta H_f (T_0 - T)] / 2.303RTT_o - \log \gamma_2$$

Solvation & association in solution of polar compounds

- Combination of solvent with the solute due to formation of hydrogen bond is called solvation causing negative deviation
- Interaction of like molecules constituting components of solution is called association resulting in positive deviation from Raoult's law.

Solubility of strong electrolytes

- Solubility of solid forming endothermic solution increases as temperature is raised while for exothermic ones the reverse is true.



Solubility of slightly soluble electrolyte

- Solubility of such solute is expressed by solubility product [K_{sp}] of the compound.

  Example: $AgCl \rightleftharpoons Cl^- + Ag^+$

$$[Ag^+][Cl^-]/\ AgCl_{solid} = K$$

$$Ag^+][Cl^-] = AgCl_{solid}\ K$$

$$[Ag^+][Cl^-] = K_{sp}$$

The concentration of each ion is raised to a power equal to the number of ions appearing in the formula

Example: $Al(OH)_{3\ solid} \rightleftharpoons Al^{+3} + 3(OH)$

$$[Al^{+3}]\ [OH^-]^3 = K_{sp}$$

Example:

The measured solubility of AgCl in water at 20°C is 1.2×10^{-5} mole/liter. Compute K_{sp}

$K_{sp} = [Ag^+][Cl^-] = (1.2 \times 10^{-5})(1.2 \times 10^{-5}) = \underline{1.44 \times 10^{-10}}$

Note: Addition of common ion reduces solubility of slightly soluble electrolyte, until equilibrium is established.

Example: What is the solubility x of AgCl in mole/liter in an aqueous solution containing 0.04 M NaCl? The solubility of AgCl product of AgCl is 1.2×10^{-10}

$K_{sp} = 1.44 \times 10^{-10} = [Ag^+][Cl^-] = x[0.04+x]$

$1.44 \times 10^{-10} = x^2 + 0.04x$

$0 = x^2 + 0.04x - 1.44 \times 10^{-10}$, since x^2 is so small,

we have $x = 3.6 \times 10^{-9}$ mol/L, disclosing reduced solubility of AgCl in water since $3.6 \times 10^{-9} < 1.2 \times 10^{-5}$ mol/L

Solubility of weak electrolytes

- Most of the drugs currently in use are either weak acids or bases
- They react with strong bases or acids
- They exist as ions over definite pH ranges
- Fatty acids containing more than 10 carbon atoms are soluble in solvents having low dielectric constants
    - Example: Oleic acid is insoluble in water but soluble in alcohol and in ether
- Hydroxy acids such as tartaric & citric acids are quite soluble in water since they are solvated via their hydroxyl groups

- Aromatic acids react with dilute alkalies to form water soluble salts. However, they precipitate out as the free acids if stronger acidic substances are added to their solution **or** as heavy metal salts upon addition of ions of heavy metals

Example: Phenol [slightly acidic] is soluble in NaOH solution

$$C_6H_5OH + NaOH \rightarrow C_6H_5O^- + Na^+ + H_2O$$

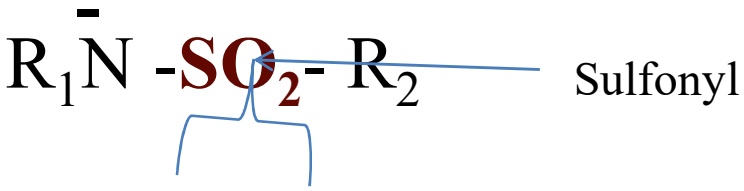
✓ Salicylic acid is soluble in alkalies & alcohol. Its OH is engaged in intermolecular hydrogen bond formation, hence never contribute to salicylic acid solubility.

✓ Phenol is weakly acidic & only slightly soluble in water but is quite soluble in dilute NaOH. Phenol is weaker than H_2CO_3 & is thus displaced from its dilute alkali solution by CO_2. For this reason carbonates and bicarbonates cannot increase solubility of phenol in water.

- ✓ Many organic compounds containing a basic nitrogen atom in their molecule are vital in pharmacy. Most of these drugs are not soluble in water but soluble in dilute solution of acids. Addition of alkali to a solution of the salt of these compounds precipitates the free base from solution

Examples: Alkaloids, antihistamines, local anaesthetics

On the contrary the nitrogen atoms in sulphonamides and barbiturates act as weak acids due to withdrawal of electrons by strong electronegative oxygen atoms.



The influence of pH on the solubility of drugs

The solubility of weak electrolytes is strongly affected by the pH of the solution

Example:

- Phenobarbital sodium is soluble in alkaline pH range but precipitate as molecular Phenobarbital at acidic pH range
- The alkaloidal salts such as atropine sulphates precipitate from solution in alkaline pH range

Note: For maximum therapeutic effectiveness of drugs forming weak electrolytes, optimal pH in which they are soluble should be established

The influence of solvents on the solubility of drugs

- Solubility of weakly acidic or basic drugs is higher in Cosolvent than in pure water. This phenomena is called cosolvency
- The mixture of solvents such as alcohol, glycerin and water, or alcohol &water, etc are called cosolvents

Combined effects of pH & solvents on drugs solubility

Solvent affects solubility of weak electrolytes in a buffered solution in two ways:

1. Addition of alcohol to a buffered aqueous solution of a weak electrolytes increases solubility of unionized species by adjusting the polarity of solvent to a more favorable value
2. Being less polar than water alcohol decreases the dissociation of a weak electrolyte, & the solubility of the drug goes down as the dissociation constant is decreased[Pk_a is ↑ed].

Effects of surfactants [Surface-active agents]

The solubility of weakly acidic or basic drugs is increased by solubilizing effects of surfactants

Solubilization

Formation of micells around each insoluble or slightly soluble drug particles by surfactants to increase their solubility in the solvent system.

Complexation as solubility enhancing mechanism

- Complexation is a process of enhancing solubility of drug molecules using molecular complexing agents
- Complexation relies on relatively weak forces (London forces, hydrogen bonding, and hydrophobic interactions) between drug and complexing agent.
- As the concentration of the complexing agent is increased, so is solubility, up to a maximum point.
- In some cases when the complexing agent is too concentrated, the complex can precipitate out of solution as more complexing agent is added.

Examples of Molecular complexing agents

- Polymers such as PEG, methyl and carboxy methyl cellulose, polyvinyl-pyrrolidone

Influence of solid state (polymorphs, amorphous, solvates)

Polymorphism

- Existence of drug substance in different crystal forms
- One of them is stable while the rests are metastable
- Both stable & metastable forms exhibits same chemical but different physical properties
- Metastable forms have higher dissolution rate than stable forms
- Metastable form converts to stable form during shelf-life, milling, granulating, drying & /or compression operation of polymorph

➢ Powdered polymorph —Granulation→ solvation

➢ Solvated polymorph —Drying→ anhydrous polymorph

➢ Amorphous form of drugs are without regular molecular lattice arrangements

Note: Formulator should notice such potential conversion

- Distribution phenomena
  - Distribution law
  - Effect of molecular association and ionic dissociation
- Applications

Distribution of solutes between immiscible solvents

- If an excess liquid or solid is added to a mixture of two immiscible liquids, the solute will distribute itself between the two phases until saturation occurs.
- However, if the solute is added in a quantity inadequate to saturate the immiscible solvents, it will distribute between the two solvents in a definite ratio called distribution ratio , distribution coefficient or partition coefficient .If C_1 & C_2 are the equilibrium concentrations of the substance in solvent$_1$ and solvent$_2$, then: **$K = C_1 / C_2$, which is called distribution law**

Example: When boric acid is distributed b/n water and amyl alcohol at 25°C, the concentrations in water & amyl alcohol were found to be 0.0510 & 0.0155 mole/liter, respectively. Find distribution coefficient. **[Solution: K= 3.29 or 0.304].**

5. Packaging & storage of pharmaceuticals

5.1. Introduction (definitions and terminologies)

5.2. Packaging materials

5.3. Closures

5.4. Labeling pharmaceutical dosage forms

5.5. Storage, stability of pharmaceuticals & beyond use date

5.1. Introduction

Definition

Packaging is an economical means of providing presentation, protection, identification/information, containment, convenience and compliance for a product during storage, carriage, display and use until such time as the product is used or administered

Packaging refers to all operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product

Packaging Material

- Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any other packaging used for transportation or shipment
- Can be **primary or secondary** according to whether or not they are intended to be in direct contact with the product
- **Primary packaging:** has direct contact with product

  Examples: Vials, Ampoules, Bottles, Blister
- **Secondary packaging**: Has indirect contact with product

  Examples: Box, Carton

Role/function of the pack

Two primary roles of a Pack: containment & protection

Containment :

- Packaging contain product in one zone preventing it from being escaped & affected by contaminants in another zone
- Package prevents product from entering the env't and the environment from entering the product
- Package must remain functionally inert to its content
- Package never become part of product or vice versa

Protection

- Implies that the product inside does not sustain physical damage &/or chemical breakdown due to light, heat, oxygen, and water vapour
- Additional protective functions includes:
  - ❖Sterility
  - ❖Reclosure
  - ❖ Communication (via the label)
  - ❖Compliance
  - ❖Tamper evidence
  - ❖Temperature control

- Protection is almost invariably the most critical factor as it controls the total shelf-life of the product

  What to be protected?

- Protection against such factors as:
  - Mechanical
  - Climatic
  - Biological
  - Chemical

Mechanical hazards: Occurs due to

- Compression
- Vibration
- Puncture or piercing
- Shock or impact damage

➢ Minimized by cushioning, restriction of movement, more careful handling, etc

Climatic or environmental hazards

- **Moisture** [may cause physical changes (e.g. dulling, softening, hardening, etc.) or chemical change (hydrolysis, effervescence, etc.)]
- **Temperature** [Accelerate or decelerate chemical reaction rate]
- **Light [**causes photochemical change]
- **Atmospheric gases** [oxygen, carbon dioxide]

Biological hazards

Microbiological

- In sterile products, the pack and its closure must maintain a 100% effective seal against microbiological ingress, i.e. bacteria, moulds and yeasts.
- Ingress of yeasts is critical with sugar based products as fermentation may occur [e.g. syrups]

Other forms of infestation

- insects, termites, vermin, rodents

Chemical hazards

- Chemical interaction between a product and its pack [not due to chemical interaction inherent to the formulation as the later cannot normally be reduced or avoided by pack selection]
- Examples of chemical interaction between a product and its pack :
  - **Adsorption** of components such as preservative, EDTA
  - **Permeation** [such as loss of volatile preservatives]
  - **Leaching** :Releasing composition of plastic/glass container to is contents

Closures

Functions of a closure can be providing:

- **totally hermetic seal**. Permits no exchange between the contents and the env't : e.g. Fused glass ampoule
- **effective microbiological seal**

Example: Rubber bung and metal over-seal.

As rubber is permeable to moisture and gases to some degree, a bacteriological seal may not be strictly hermetic.

- **effective seal** which is acceptable to the product, i.e. a closure which is not hermetic or a total guarantee against bacterial ingress, but adequate for the product

Methods used for determination of closure efficiency

What is closure efficiency?

Ability to prevent undesirable exchanges b/n product and outside atmosphere

- Placing a desiccant in a pack stored under high RH and **detecting any moisture gain**
- Putting liquid inside the pack, storing at high temperature and low RH, and then **detecting any moisture loss as a reduction in weight**
- Holding the empty pack under water, applying a vacuum and **observing for leakage or liquid ingress**
- Conducting **leak test**

6. solutions

6.1 Introduction

Pharmaceutical solutions :

- Homogenous liquid preparations in which drug and various excipients are dissolved in the chosen solvent system **or**
- Homogenous molecular dispersion of two or more substances

Components of solution : solute(s) and solvent

- Solute :gas, liquid or solid that are dissolved or dispersed in solvent as molecules or ions throughout the solvent
- Solvent: Major constituents of a solution

6.2 Dissolution & solubility

Dissolution

- Mass transfer process where by solid solutes are dissolved into solution or
- Transfer of molecules or ions from solid state to solution

Dissolution rate refers to amount of solute that goes into solution per unit time

Solubility

- Extent to which dissolution proceeds under a given set of experimental conditions
- Amount of solute that passes into solution when equilibrium is established b/n solution & excess (undissolved) substance such that saturated solution is formed.

Factors affecting solubility

- Temperature [eg: KNO_3 vs Na_2SO_4]
- Molecular structure of solute
- Nature of solvent
- Polymorphism
- Particle size

6.3. Ingredients [components]of solution

Formulation of solution =

Drug + Inactive pharmaceutical agents

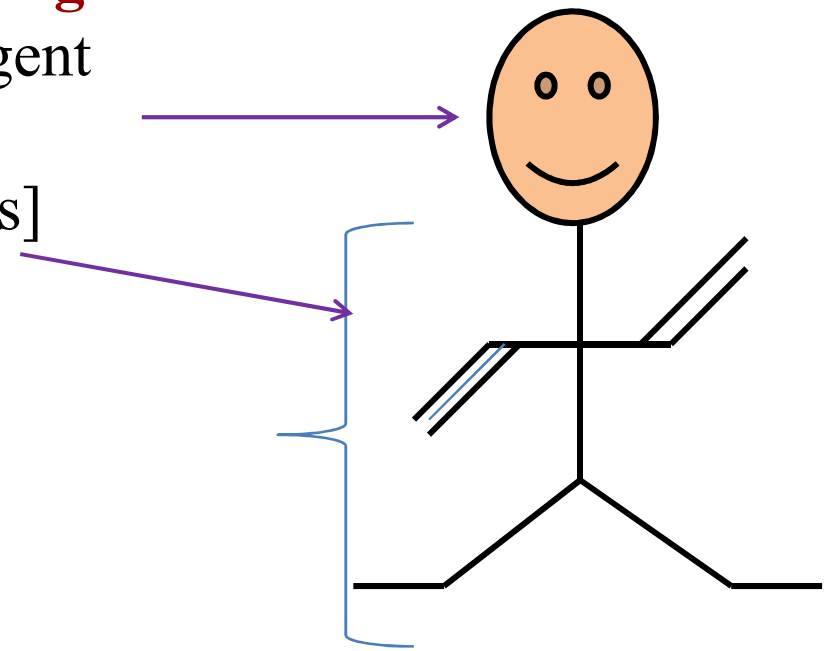
❖ Drug is active pharmaceutical agent

Inactive pharmaceutical agent

❖ Solvent [aqueous or nonaqueous]
or Cosolvent

❖ Additives

- Antioxidant
- Preservative
- Chelating agent
- Buffer solution
- Organoleptic agents
- Tonicity adjusting agent



6.4 Methods of preparation of solution

- Percolation method
- Heat method
- Agitation method

6.5 Solutions taken orally

- Non-sterile oral liquid dosage forms

Advantages of oral solution

- ❖ Have ease of administration to individuals who have difficulty in swallowing , e.g. elderly patients, infants
- ❖ Faster bioavailability of therapeutic agent than from solid oral dosage forms of same drug provide that no drug precipitation occurs in the git fluid
- ❖ Uniform dosage is possible
- ❖ Safe to administer those drugs that induce local irritation if taken in solid state. Eg: KI, KBr

Disadvantage of oral solutions

- Less stable than solid dosage forms of same drug
- Taste-masking may be difficult for bitter drugs
- Bulky [Expensive to ship & inconvenient to carry]
- Dose measuring device is required
- Inter-patient variability in dose measuring
- Total loss due to accidental breakage
- Difficult to make solutions of poorly soluble drugs
- Support microbial growth, if not preserved

Types of oral solutions

Swallowable solutions

- ❖Syrups
- ❖Elixirs
- ❖Linctuses
- ❖Draughts

Solutions used in the mouth

- ➢Mouthwashes
- ➢Gargles
- ➢Throat paints & sprays

Syrups

- Sweet viscous & concentrated aqueous solutions
- Can be medicated or non-medicated preparations

Non-medicated syrup

- Contains no therapeutic agents
- Classified into simple syrup or flavoured syrup
  - Simple syrup: contains sucrose dissolved in purified H_2O
  - Flavoured syrup: simple syrup + flavouring agent
- Used as a vehicle to prepare medicated solution

Medicated syrup = **Drug** + **Vehicle** + Sucrose + **Adjuncts**[additives]

= Simple syrup + Drug

= Flavoured syrup + Drug

- Concentration of sucrose must be 65% w/w or 85% w/v

Reasons:

i. Minimize microbial contamination

ii. Bacteriostatic by virtue of their osmotic effect

- Polyols [Alcohol, glycerol or sorbitol] are added to syrup
  - ➢ Act as co-solvent
  - ➢ Retard crystallization of sucrose
  - ➢ Improves dissolution rate of other ingredients

Elixirs

- Clear brilliant,sweetened,flavoured,preserved hydro-alcoholic solutions
- Classified as medicated & non-medicated elixir
- Contain more alcohol & less sugar as compared to syrup, subsequently:
  - ✓Less sweet & viscous
  - ✓Has less bitter taste masking effect

Example:

- Ephedrine elixir
- Phenobarbital elixir

Linctuses

- Viscous preparation usually prescribed for relief of cough
- Usually consist of a simple solution of active agent in a high conc. of sucrose, often with other sweetening agents
- Agents with sedative or expectorant action can be used

Example: Codeine phosphate linctuses

Draughts: Single liquid oral dose

Example:

✓ Piperazine [Warmin] adult dose

✓ Ipecacuanha Emetic draught B.P.C

6.6 Solutions used in the mouth and throats

A.Mouthwashes

Used for cleansing &/or deoderizing purposes

Composition

1. Antibacterial agents

- ✓Alkaline phenol mouth wash
- ✓Hydrogen peroxide

2. Astringents

- ✓Zinc sulfate or Zinc chloride mouth wash
- ✓Compound NaCl mouth wash [NaCl + $NaHCO_3$ + Chloroform water + peppermint]

B. Gargles

- Used to relief soreness in mild throat infection
- Have deodorant effect , : Example

Phenol gargle

✓ Potassium chlorate & phenol gargle

- Has weak astringent action
- Stimulate flow of saliva

- Has anaesthetic action

Note:

- MW & gargles contain antiseptic, analgesic & astringent
- Used directly or diluted with warm water
- Astringent makes the skin tissues contract & harden

C. Throat paints

- Used for mouth & throat infections
- Applied by throat brush

Example

✓ Compound Iodine paint {Mandl's paint} for pharyngitis & tonsillitis

✓ Crystal violet paint used for thrush

D. Throat sprays

Uses

- For treatment of laryngitis, tonsillitis or pharyngitis
- To relief asthma & hay fever by acting as bronchial relaxant
- Applied using atomizer or nebulizer

Example:

Adrenaline & Atropine spray, Compound B.P.C

6.7 Solutions instilled into body cavities

- Douches
- Enemas
- Ear drops
- Nasal drops
- Eye drops

Douches

- Medicated solutions for rinsing body cavity such as vagina[Vaginal solution or irrigation] , bladder [Bladder irrigation]
- Usually supplied in their concentrate form for later dilution with warm water at the time of use

Purpose	**Example**
1. Antiseptic :	Chlorhexidine 0.02%
2. Astringent :	1% Alum
3. Cleansing agent:	Isotonic NaCl solution

N.B. Bladder irrigations or vaginal irrigations[to be used post-delivery] must be sterile & isotonic with tissue fluid

Enemas

- Aqueous or oily solutions/emulsions / suspensions for rectal administration of medicaments

Uses

- Cleansing purposes
- Diagnostic
- Therapeutic

Cleansing enema

Used to evacuate faeces in constipation or prior to operation

Cleansing mechanisms

1. Stimulate peristalsis of impacted faeces

- due to their **large volume** [0.5 to 1 lt]

  Eg.: Plain water, soap[1 in 20] & Turpentine enema

- Cause **osmotic retention** of water in the bowel despite their small volume

  Eg.: Na_3PO_4 enema(100 ml) , Mg SO_4 enema

2. Lubricate impacted faeces

Eg: Olive & Arachis oil enemas[100 to 500 ml]

Therapeutic enema

Uses

- Sedatives : Chloral hydrate, paraldehyde
- Anthelmintics
- Anti-inflammatory agents: Corticosteroids for ulcerative colitis
- Nutrients: when absorption by mouth is impaired

Diagnostic enema such as BaSO4 enema

- Used for X-ray examination of lower bowel

Ear drops [otic]

- Simple solutions of drugs in water, propylene glycol , glycerol, or alcohol/water mixtures for local use
- Applied to the external auditory canal as drops, sprays or washes

Uses of Aural products:

- Treating mild ear infection, eg. CAF ear drop
- Softening wax eg.: H_2O_2
- Cleansing after infections : 0.9% NaCl
- Drying weeping surfaces
- Antisepsis & anaesthesia : Phenol

Nasal drops

- Formulated as small-volume solutions in an aqueous vehicle, but not oils
- Formulated at pH 6.8 since buffering capacity of nasal mucus is low
- Should be isotonic with nasal secretions using 0.9%NaCl and have same viscosity with nasal mucus
- Include such active agents as:
  - Anti-inflammatory
  - Antibiotics
  - Decongestants

Note: Nasal drops should not interfere with cleansing capacity of epithelial cilia of nasal mucosa

Eye Drops

- Sterile and isotonic aqueous or oily solutions
- Preserved if multidoses
- Its optimum pH equals that of tear flui7.4

6.8 Topical solutions [External solutions]

1. **Collodions**
2. **Liniments**
3. **Lotions**
4. **paints**

Collodions

- After evaporation of the solvent leave a tough, flexible film that will seal small cuts or hold a drug in intimate contact with the skin
- Film former is usually pyroxylin (nitrocellulose) in an alcohol/ether or alcohol/acetone solvent blend
- Often castor oil as a plasticizer & colophony resin as an adherent are incorporated into formulation

Types of collodion

1. Flexible collodion B.P

- Solution of pyroxylin, colophony & caster oil in a mixture of ether & alcohol

2. Salicylic acid collodion B.P.C

- Flexible collodion plus 12 % salicylic acid
- Used to dissolve corn & wart

Note

- Store in light-resistant, well-closed container
- Labelled for external use only
- Store in a cool place
- Keep away from naked flame since it is inflammable

Liniments

- Oily, alcoholic, soapy or emulsified external preparation
- Intended for massage into the skin
- Contain such ingredients as analgesic, rubefacient[Substance that cause the skin to become red], smoothing or stimulating properties
- Should not be applied to wound or broken skin

Example

✓ Methyl salicylate liniment

✓ Camphor Liniment as counterirritants

Lotions

- Designed to be applied to the skin without friction
- May contain humectants, so that moisture is retained on the skin after application of the product, or alcohol, which evaporates quickly, imparting a cooling effect and leaving the skin dry
- Have soothing effect
- Applied by dabbing or after spreading on a dressing without friction

Example

- ✓Salicylic acid lotion
- ✓Benzoic acid compound lotion

Paints

- Liquids for application to the skin or mucous membranes
- Applied with a small brush in small amounts
- Solvent [alcohol, acetone or ether] evaporates quickly leaving therapeutic film on the skin
- Glycerol is often added to modify viscosity & ensure prolonged contact with the skin

Example

- ✓Crystal Violet Paint
- ✓Coal Tar Paint

6.9. Parentral solutions or injectable solutions

- Parenteral is derived from the two words “para” and “enteron” meaning to avoid the intestine.
- Defined “as those preparations intended for injection through the skin or other external boundary tissue
- Sterile solutions for injection or infusion into body
- Prepared scrupulously so that they are sterile, free from pyrogen & particulate matter
- Injections are overfilled with small excess over labelled volume to ensure that the required volume can be obtained from the product

Advantages

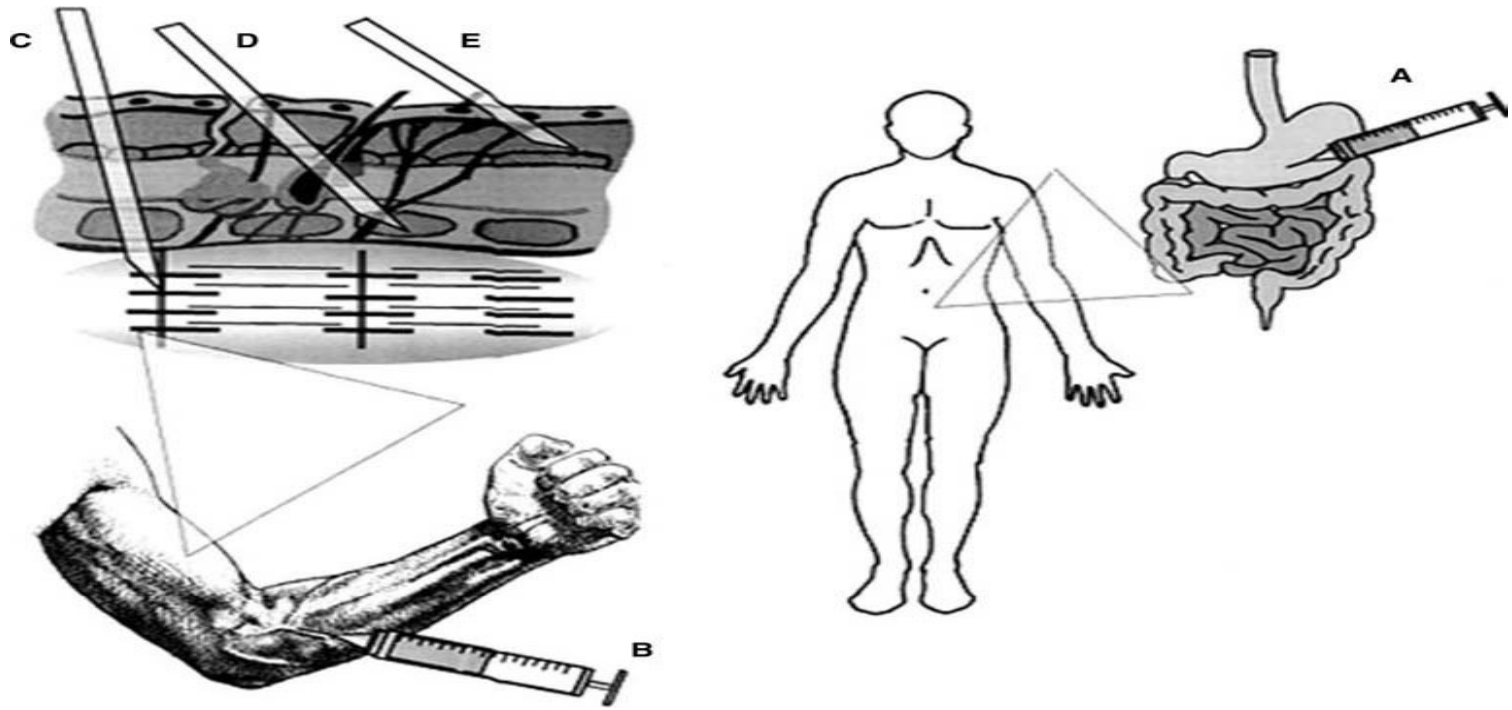
Useful for:

- patients who cannot take drugs orally
- drugs that require a rapid onset of action (primarily intravenous administration) for emergency situations
- providing sustained drug delivery(implants, intramuscular depot injections)
- self-delivery of drugs (subcutaneous)

- injection of drugs directly into a tissue (targeted drug delivery)
- drugs that are inactivated in the git or susceptible to first-pass metabolism by the liver
- delivering fluids, electrolytes, or nutrients (total parenteral nutrition,TPN to patients)
- providing precise drug delivery by intravenous injection or infusion utilizing pharmacokinetic techniques

Disadvantage

- Require specialized equipment, techniques & devices to prepare and administer drugs
- More expensive and costly to produce & use
- Difficult to reverse drugs' effects after administration
- Potential for:
  - ✓ infection, pain & tissue damage at site of injection
  - ✓ sepsis
  - ✓ thrombo-phlebitis
  - ✓ fluid overload
  - ✓ air embolism
  - ✓ extra-vasation



A=intra-peritoneal
B= Intravenous
C= Intramuscular
D= Subcutaneous
E= Intradermal

Types of parenteral products

Classified in to two based on their volume

Small volume parentral {SVP}

- 100 ml or less than 100 ml solution
- provided as a single-dose or multidose product

Large Volume Parentral{LVP}

- Intended to be used intravenously
- Contain more than 100 ml of solution
- Provided as a single-dose injection or IV infusion

- Therapeutic goal of LVPs is to provide electrolytes, body fluids, and nutrition
- May or may not be isotonic with blood depending upon concentration of components, which include sodium chloride, dextrose, mannitol, Ringers (sodium, potassium, calcium, and chloride) and Lactated Ringers (calcium, potassium, sodium, and lactate), sodium bicarbonate, ammonium chloride, sodium lactate, fructose, alcohol, dextran,& amino acids.

Note: SVPs and LVPs are often combined during the extemporaneous preparation of Intravenous admixtures

Composition of parenteral products

- Drugs
- Excipients
  - ❖Buffers
  - ❖Solvents /cosolvents
  - ❖Antimicrobial preservatives
  - ❖Antioxidants
  - ❖inert gases
  - ❖Surfactants
  - ❖Complexation /Chelating agents

Note: Coloring, flavouring & sweetening agents are prohibited from parenteral products

Liquids used for preparation of injections

Water for Injection, USP

- Not required to be sterile but must be pyrogen-free

Sterile Water for Injection, USP

- Sterilized WFI
- Contains no preservative or antimicrobial agent
- Pyrogen-free
- Provided in single containers no larger than 1000 ml.
- Used for reconstitution of other parenteral products

Bacteriostatic Water for Injection, USP

- sterile water containing one or more preservative or antimicrobial agent
- Packaged in prefilled syringes or vials not > 30 ml.
- Used in the reconstitution of SVPs.

Limitation presence of the antimicrobial agent is contraindicated in newborns.

Other solvents for parenteral formulations

Sodium Chloride Injection,USP

Bacteriostatic Sodium Chloride Injection, USP

Ringers Injection, USP, and Lactated Ringer's, USP.

Preparation of parenteral solutions packaging

- All parenteral products must be produced under strict, current good manufacturing practices (cGMP) to ensure final product is sterile & pyrogen-free

Sterilization

- Complete destruction of all living organisms or their spores or the complete removal from the product

6.10. Types of sterilization methods

- Steam sterilization
- Dry-heat sterilization
- Filtration sterilization
- Gas sterilization
- Ionizing-radiation sterilization

Packaging of parenteral solutions

- Single dose container

  Example: Ampoule, PVC bag

- Multiple dose container

  Example: Vial

Unit 7: Rheology

- Introduction
- Newtonian systems
- Non-Newtonian systems
- Thixotropy
- Determination of viscosity
- Viscoelasticity

Introduction

- R*heology* is the **science of flow or deformation** under stress
- *Viscosity* is resistance fluidity
- Rheology is involved in mixing and flow of materials, their packaging into containers, and their removal prior to use.
- Rheology of a particular product affects acceptability of the product to the patient, its physical stability, and bioavailability by affecting rate of drug absorption from git and dosage forms

- Depending upon their flow properties fluids can be classified into Newtonian & Non-Newtonian fluids
- **Newtonian fluid**: involves a direct proportionality of shear stress[F/A] and shear rate [dv/dx] for all values of shear

$$Shearing\ stress = \eta \times \text{Shear rate}$$

$$F/A = \eta dv/dx \text{ , where}$$

F/A = *shearing stress* ($dyne.cm^{-2}$)

dv/dx = *shear rate* (sec^{-1})

η = *coefficient* of viscosity or simply viscosity

[($g.\ cm^{-1}.\ sec^{-1}$ = poise or $dynes.sec.cm^{-2}$)]

Example: Solution, hydrophilic colloids

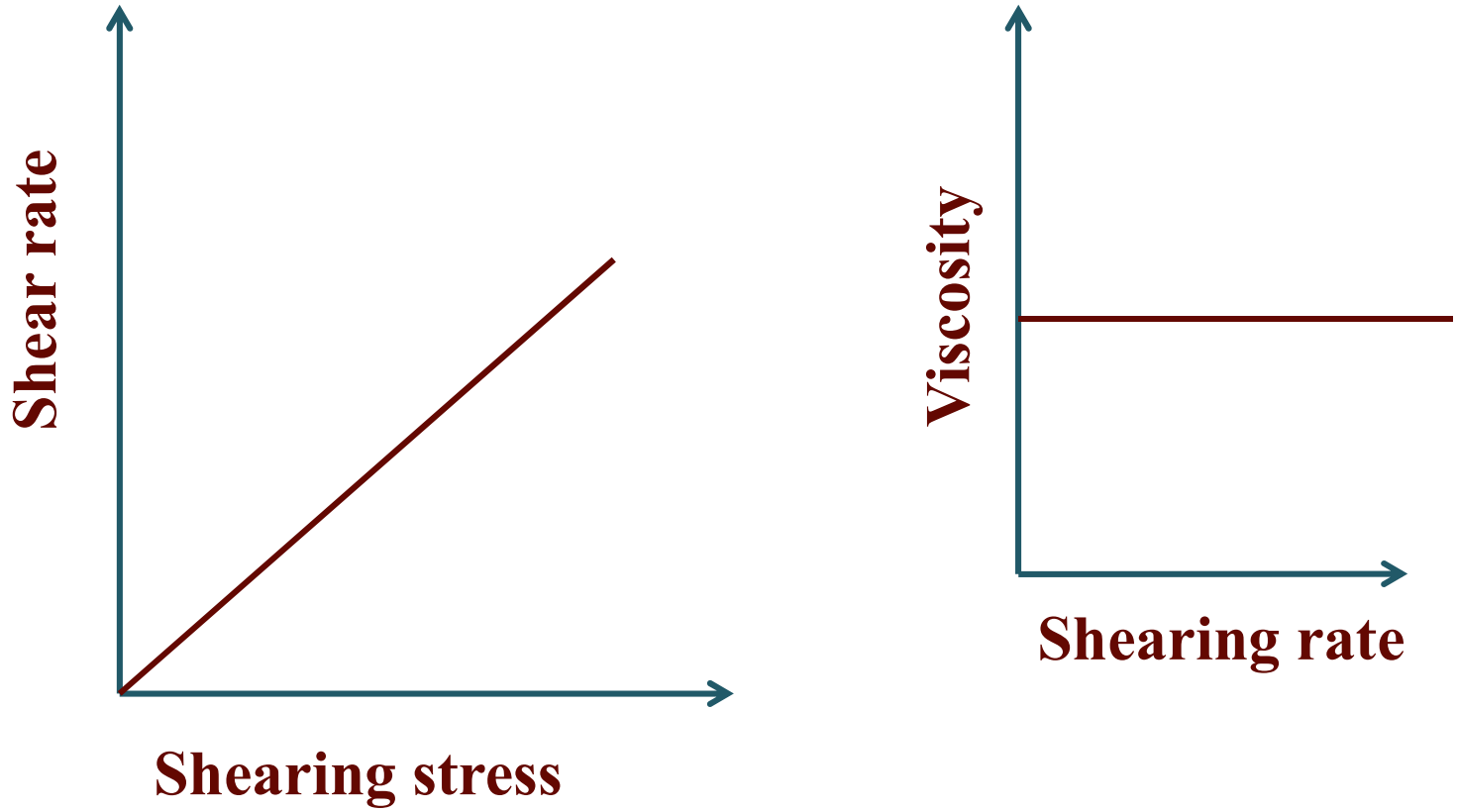


FIGURE 7.1 Flow curve [Rheogram] for a liquid displaying a Newtonian flow

Non-Newtonian fluid: Fluid flow having no direct proportionality between shear stress and shear rate **or** The shear stress necessary to achieve a given shear rate may increase more rapidly or less rapidly than is required by the Newtonian fluid

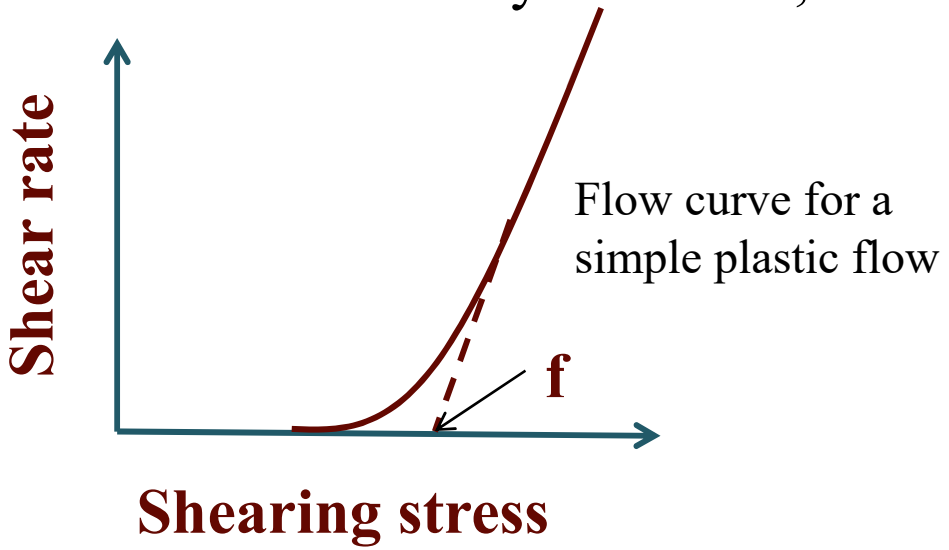
Examples: Colloidal solutions, emulsions, ointments, liquid suspensions and solid heterogeneous dispersions

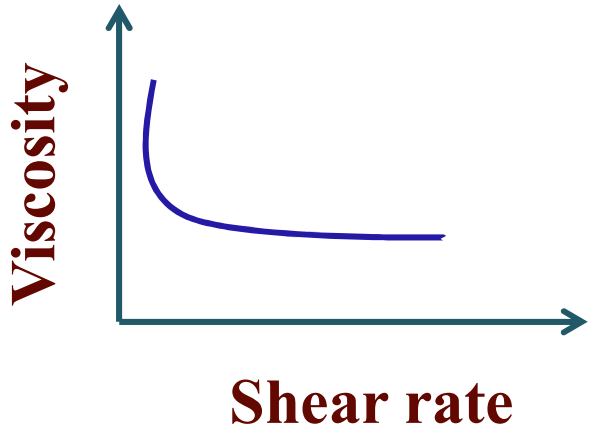
Types of Non-newtonian systems

1. Plastic flow
2. Pseudo-plastic flow
3. Dilatant flow

Plastic flow

- Substance that exhibit plastic flow are called Bingham bodies
- A plastic material does not flow until a certain minimum shearing stress called yield value is exceeded.
- Plastic flow curve does not pass via the origin but intersects the shear stress axis at a point.
- At stress below yield value, a material acts like elastic material

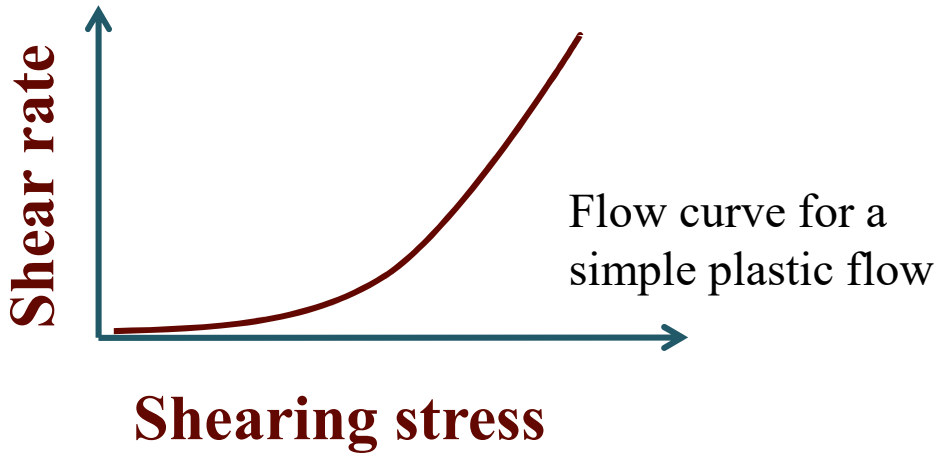




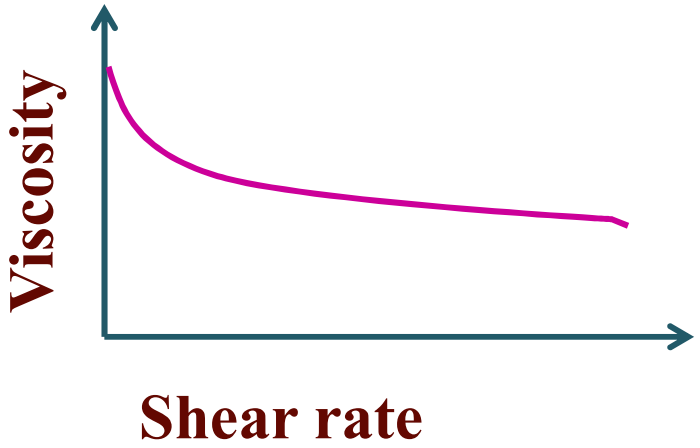
Pseudo plastic flow: displays decreasing viscosity with increasing shear rate , thus sometimes it is called shear-thinning.

Pseudoplastic substances begin to flow when a shearing stress is applied, disclosing no yield value

Reason: Molecules of such preparation are arranged randomly at rest with high friction & orderly when at motion with low friction. **Examples**: paints, emulsion, and dispersions of many types



Flow curve for a simple plastic flow

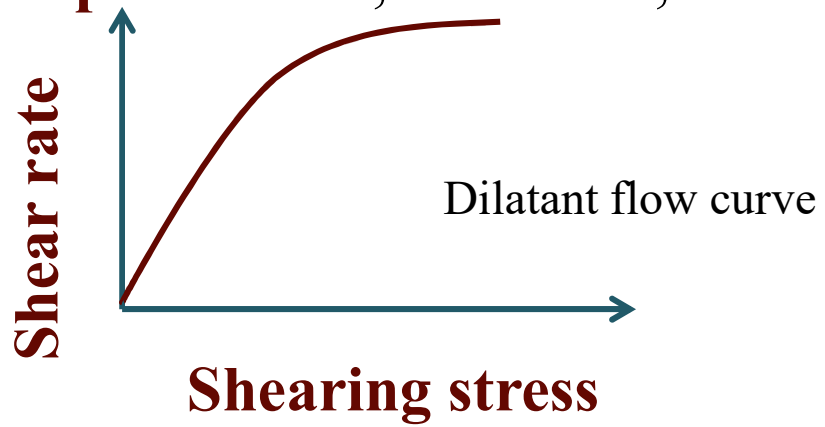


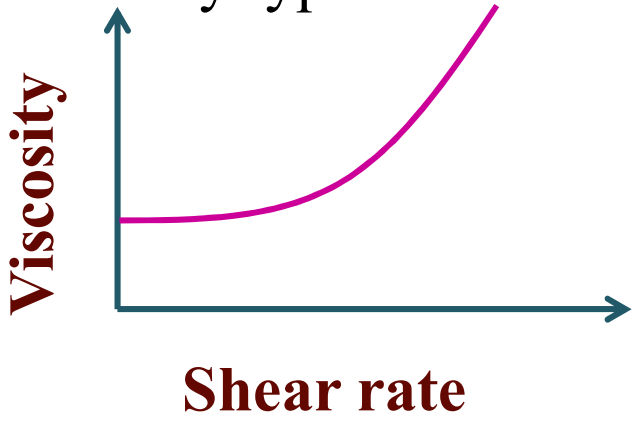
Dilatant flow: Exhibits an increase in viscosity as the shearing stress is increased. Sometimes it is called shear-thickening system. Characterized by. Upon shearing their volume increase

Example: Concentrated suspensions and zinc oxide thus

Reason: At rest, dispersion medium surrounding each particles reduce resistance to flow while during shearing the particles are rearranged displacing the dispersion medium from around the particles and triggering increased friction b/n particles & increased resistance to flow.

Examples: Paints, emulsion, and dispersions of many types





Thixotropy

- Reversible gel-sol transformation
- Thixotropic fluid undergoes a decrease in viscosity with time during constant shearing. Flow occurs when the yield value is exceeded, and the viscosity decreases as the rate of shear increases

Examples : Aluminum hydroxide gel , starch gel and bentonite magma

Determination of viscosity of fluid

A. Capillary Viscometer

- Viscosity of a Newtonian liquid can be determined by measuring time required for liquid to pass b/n two marks as gravity causes it to flow through a viscometer such as Ostwald viscometer
- The time of flow of the liquid under test is compared with the time required for a liquid of a known η to pass b/n the two marks. If η_1 , ρ_1 & t_1 are viscosity, density and flow time of unknown liquid and η_2 , ρ_2 & t_2 are viscosity, density and flow time of the reference standard liquids, then the absolute viscosity of the unknown liquid, η_1, can be determined using the following equation :

$$\eta_{1/}\,\eta_2 \quad = \rho_1 t_{1\,/}\,\rho_2 t_2$$

Example

At 25°C water has a density (ρ1) of 0.997 g/cm3 and viscosity (η) of 0.00895 poise. The time of flow of water in a capillary viscometer is 10 sec. A 65% sucrose solution requires 890 sec, and its density (ρ2) is 1.313 g/cm3. The viscosity of the 65% sucrose solution can be determined

Falling Sphere Viscometer [Eg: Hoeppeler viscometer]

- A glass or a steel ball rolls down an almost vertical glass tube containing test liquid at a known constant temp.
- Falling rate of the ball is inversely related to η the liquid.
- The test liquid & the ball are placed in the inner glass tube & allowed to reach temperature equilibrium with water in the surrounding constant temperature jacket
- The tube and the jacket are then inverted, which puts the ball at the top of the inner glass tube. The time it takes the ball to fall b/n two marks is accurately measured.

- Viscosity of Newtonian liquid is then calculated from the following equation:

$$\eta = t[S_b - S_f]B$$, where

- t = time the ball takes to fall b/n two points,
- Sb and Sf = specific gravities of the ball and the liquid being tested.
- B = constant for a particular ball, and its value is supplied by the manufacturer

Example: A ball of density 3.12 takes 109 sec. to fall fixed distance of inclined tube viscometer when a calibrating liquid of density 0,94 & viscosity 8.12 poises is used.

1. Determine instrumental constant and
2. Compute a viscosity of a sample oil of density 0.88 if the fall time under similar conditions was 125 sec.

Solution

$\eta = B[Sb-Sf]t$

$B = \eta / [Sb-Sf]t$

$= 8.12 \text{ poise} / [(3.12 - 0.94)109] \text{ g/ml .sec}$

$= 00342 \text{ poises g-1 ml sec-1}$

$\eta \text{ oil} = B([Sb-Sf]t = 0.314(3.12-0.88) 125 = 9.57 \text{ poises}$

Viscoelasticity: The continuum of the limits of the elastic deformation and pure viscous flow

Pharmaceutical uses of rheology

A. Characterizing the ease of :

- ❖ pouring & or squeezing product from container
- ❖ Maintaining product shape in a jar or after extrusion
- ❖ Rubbing product into & onto skin
- ❖ Pumping product from mixing & storage to filling equipment

B. Determining product attributes are retained during its shelf-life

8: Emulsions

8.1. Introduction

8.2. Pharmaceutical application of emulsion

8.3. Determination of emulsion types

8.4. Theories of emulsification

8.5. Formulation & preparation of emulsions

8.6. Preservation of emulsions

8.7. Rheological properties of emulsions

8.8. Physical stability & evaluation of stability of emulsions

8.1. Introduction

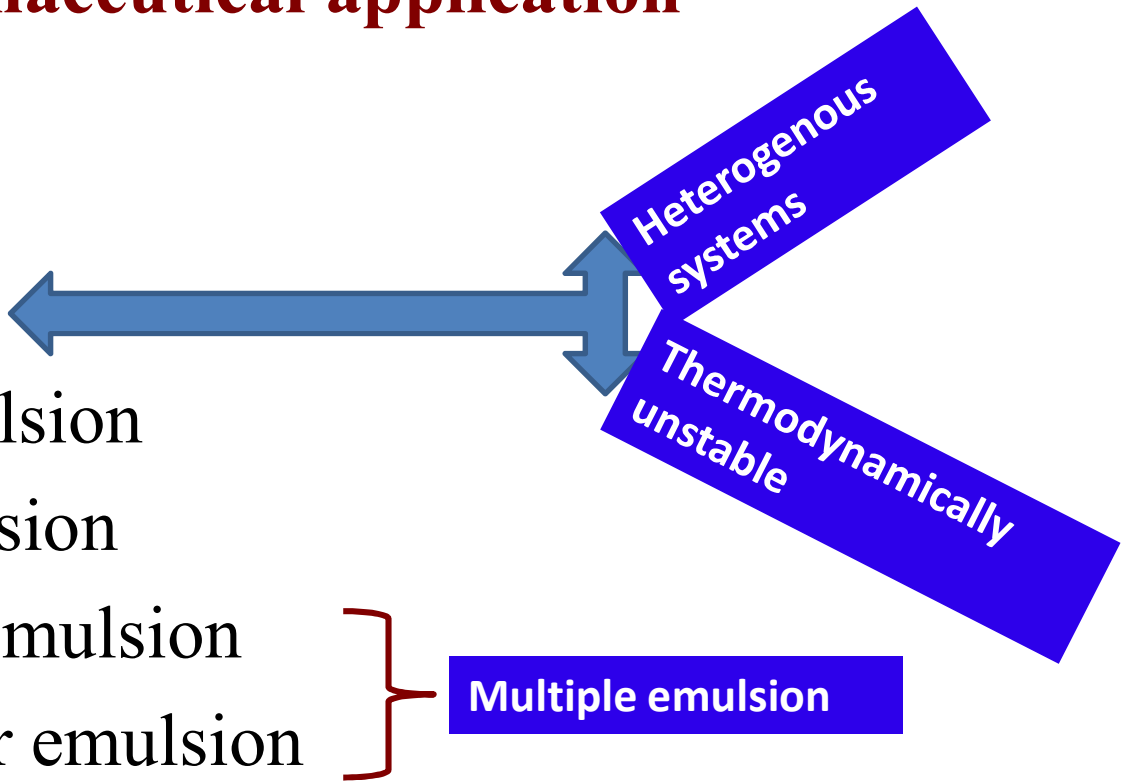
- An emulsion is a disperse system consisting of two immiscible liquid phases, as :
  - ➢Dispersion medium /continuous phase/external phase
  - ➢Dispersed phase/discontinuous phase/internal phase
- The immiscible phases usually consist of water & oil
- Emulsions are thermodynamically unstable and revert back to separate oil and water phases by fusion or coalescence of droplets
- Phase separation should be kinetically stabilized by a third component called emulsifying agent[emullgent].

8.2. Types & pharmaceutical application of emulsion

Types of emulsion

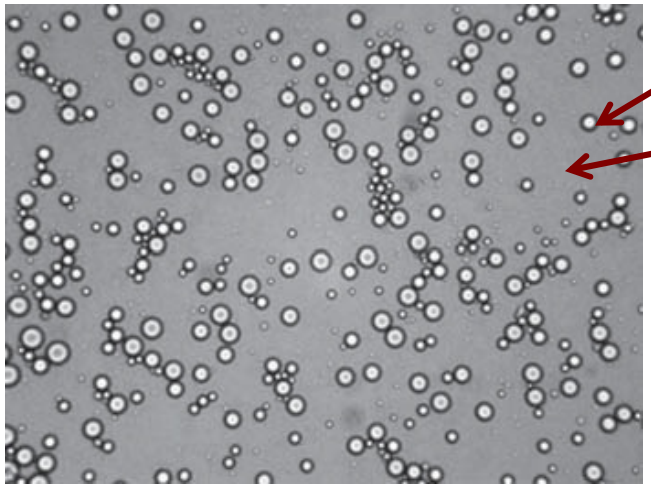
❖ Coarse emulsion

- Oil /water emulsion
- Water/oil emulsion
- Oil/water/ oil emulsion
- Water/oil/water emulsion



❖ Microemulsions

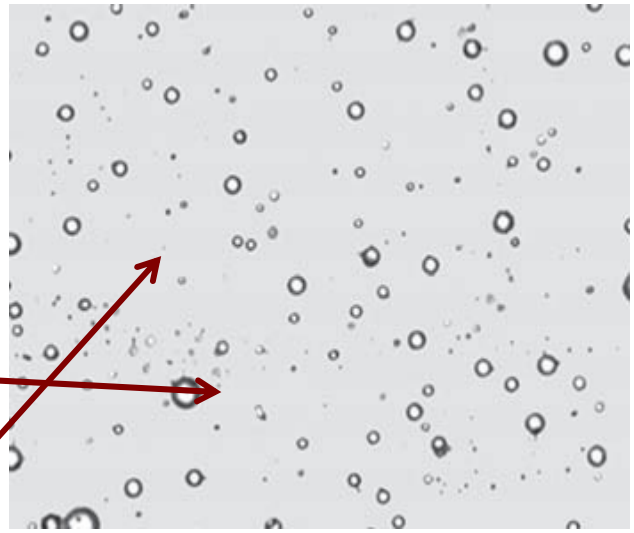
- Homogeneous systems
- Thermodynamically stable



Oil droplet

Water

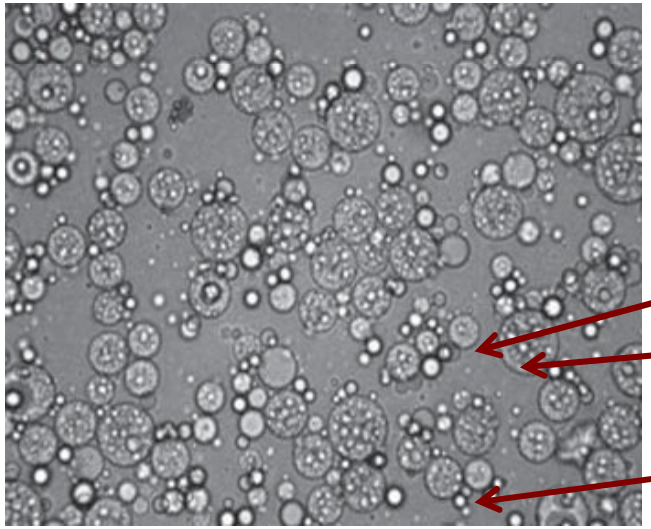
oil-in-water emulsion



Water droplet

Oil

water-in-oil emulsion



Water droplet in oil droplet

Oil droplet

Water

water-in-oil-in-water emulsion

Pharmaceutical applications of emulsion

- **Delivering drugs** with low aqueous solubility
- Masking **unpalatable taste** of drugs
- **Administering oils** that may have a therapeutic effect such as paraffin for its cathartic [purgative or laxative] effect
- Minimizing irritant effect of drug by incorporating in the internal phase of topical emulsion
- To formulate **total parentral nutrition**
- **Facilitating drug permeation** via the skin [Occlusive properties or penetration enhancer]
- Administering medication to patients unable to swallow **solid dosage** forms

Note

Routes of emulsion administration can be topical ,oral or parentral

Route of administration	Types of emlsion
Topical	W/O
Oral	O/W
Parentral	Depends on route of administration
IV	O/W
IM or SC	O/W, W/O

8.3. Determination of emulsion types

- Dominance of polar or non-polar character of emulgent determines type of emulsion produced
- Type of emulsion formed is a function of the relative solubility of emulsifying agent, the phase in which it is more soluble being the continuous phase[Bancroft rule].
- Thus,polar Emullgent form O/W while nonpolar ones form W/O emulsion

Several tests are available to distinguish types of oils.

1. **Miscibility tests**
2. **Dye method[Staining method]**
3. **Electrical conductivity method**

Miscibility tests

Principle: Upon addition of unlimited amount of liquid forming the continuous phase, emulsion remain stable**.** Accordingly:

1. If excess water is added to o/w emulsion, then it remain stable, however, it will not remain homogeneous upon addition of unlimited oil since the latter will separate via coalescence.
2. Water-in oil remain stable upon unlimited dilution of oil but never remain homogeneous upon unlimited addition of water

Unknown preparation	Liquid added in excess	Effect on phases of unknown preparation	Conclusion about the Unknown preparation
X in Y	Oil	Remain stable	Water in oil
Y in X	Water	Coalescence of globules	Water in oil
M in W	Oil	Agglomeration of globules	Oil in water
W in M	Water	Homogenous & remain stable	Oil in water

Dye method[Staining method]

Principle: Dye soluble in oil or water but not in both is used, accordingly, the phase in which the dye appeared forms the oil phase if the dye is oil soluble or the water phase if the dye is water soluble

Example: Scarlet red is soluble in oil but not in water while the reverse is true for Methylene blue

Preparation	Dye	Appearance under microscope		Conclusion
		Internal phase	External phase	
X in Y	Scarlet red	Red	colourless	Oil in water
Y in X	Scarlet red	colourless	Red	Water in oil

Electrical conductivity technique

Principle: Water is a good conductor while oil is a non-conductor of electricity

Unknown preparation types	State of the lamp	Conclusion about the types of preparation
X in Y	Gives light	Oil in water
Y in X	Gives no light	Water in oil

Bancroft rule

- Dominance of polar or non-polar character of emulgent determines type of emulsion produced
- Type of emulsion formed is a function of the relative solubility of emulsifying agent, the phase in which it is more soluble being the continuous phase.
- Thus polar Emullgent form O/W while non-polar ones form W/O emulsion

8.4. Theories of emulsification

The most prevalent theories of emulsification include:

- Surface tension theory of emulsification
- Oriented-wedge theory of emulsification
- Plastic or Interfacial film theory of emulsification

Surface tension theory of emulsification[STE]

- If two or more droplets of same liquid come together, their tendency is to coalesce to form relatively larger drop with smaller surface area than total surface area of individual drops
- The force causing each liquid droplets to resist breaking up in to smaller particles is called interfacial tension
- **According to STE**, use of emulsifiers & stabilizers [SAA]
  - lowers interfacial tension of two immiscible liquids
  - Lowers repellent force b/n dissimilar liquids drops
  - Diminish each liquids attraction for its own molecules

Oriented-wedge theory of emulsification

- It assumes that monomolecular layers of emulsifying agent curved around a droplet of the globules of the emulsion
- Hydrophilic & lipophilic portions of SAA molecules are oriented themselves facing water & oil phase respectively.

Plastic or Interfacial film theory of emulsification

- Places emullgent at the interface b/n oil & water, surrounding droplets of the internal phase as thin layer of film adsorbed on the surface of drops.
- The film prevents contact & coalescence of dispersed phase
- The tougher & more pliable the film is the greater the stability of the emulsion

8.5. Emulsifying agents

- There is a positive interfacial tension between the internal & external phases which makes emulsion thermodynamically unstable
- Collision of unprotected globules triggers coalescence ,eventually resulting in breaking or cracking of emulsion.
- Such emulsion instability can be minimized by using emulsifying agent or emullgent
- **They reduce interfacial tension b/n oil & water**, minimizing surface energy via formation of globules

Categories of emulsifying agents

Basically there are three classes:

Categories	Examples
Amphipaths	Soaps, long chain amines & alcohols
Hydrophilic colloids	Acacia , sodium alginates, gelatine, MC
Finely-divided solids	Magnesium & Aluminum hydroxides, Bentonite

Note:

- All are surface active agents
- All are adsorbed at the water-oil interface to reduce interfacial tension
- Amphipaths are stronger than hydrophilic colloids in minimizing interfacial tension

How emullgent stabilize emulsion?

Emulsifying agents assist in the formation of emulsion by three mechanism

1. Reduction of interfacial tension- thermodynamic stabilization [reduction of interfacial tension lowers interfacial free energy produced upon dispersion]
2. Formation of a rigid interfacial film-mechanical barrier to coalescences by forming film on each globules
3. Formation of electrical double layer-electrical barrier to collusion of particles & hence to coalescence

Hydrophile-Lipophile balance (HLB) of surfactants

HLB is a measure of the relative contributions of the hydrophilic and lipophilic regions of the molecule

- The HLB number of a surfactant is calculated according to an empirical formula.
- For non-ionic surfactants the values range from 0 -20 on an arbitrary scale
- Surfactants with high HLB value are hydrophilic and act as solubilising agents, detergents or o/w emulsifiers while those with low ones act as antifoaming agents or w/o emulsifiers
- In general, water-soluble surfactants stabilise o/w emulsions and water-insoluble surfactants stabilise w/o emulsions.

Example: Hydrophilic polymer stabilize emulsion by:

- Forming multilayer around each globules at interface
- Increasing viscosity of external phase [o/w emulsion]
- Imparting charge to the film if the polymer bear charge .Thus, increasing zeta-potential among particles [Electrical double layer]

- The initial stage in the preparation of emulsion is selection of appropriate emullgent
- Emulsifying agents are surfactants with HLB values of 3-6 [lipophilic] or 8 -18 [hydrophilic]
- Emulsifying agents are used to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations

Criteria for selection of emulsifier

The emullgent must :

- ❖ Be compatible with other ingredients
- ❖ Not interfere with stability or efficacy of therapeutic agent
- ❖ Be stable & do not deteriorate in the preparation
- ❖ Be non-toxic wit respect to its intended use & amount to be used by the patient
- ❖ Be capable to promote emulsification & maintain stability of emulsion for the intended shelf-life

- In practice, combinations of emulsifiers rather than single agents are used. **Why ?**
- Combination of emullgent with suitable HLB values are used since HLB values are additives fixed by blending SAAs

Example:

If 36 ml of an HLB of 15 is required, two surfactants with HLB values of 16 & 12 can be blended in a 3:1 ratio, respectively as follow:

0.75 x16 = 12 & 0.25 x12 = 3

Thus, blend 3 parts of SAA with HLB values of 16 & & 1 part of SAA with HLB values of 12 to obtain a mix of emullgent with total HLB value of 15 [12+3 = 15]

How much ml do you measure from each SAA, then ?

8.6.Formulation & preparation of emulsion

Formulation of emulsion

= Drug + Water + Oil + Emulgent + Additives

Components of formulation of emulsion

- Water
- Oil
- Emullgent

Unavoidable components

- Additives
  - Preservative
  - Antioxidant
  - Buffer

Used conditionally

Preparation of emulsion

- Emulsion never formed spontaneously
  - ✓Requires several processes to break up internal phase into globules & stabilize them in external phase
- Requires selection & control of physical & chemical criteria

Physical parameters	Chemical parameters
➢Heat	➢ Chemical compatibility & stability of ingredients
➢Temperature	➢ Selection of lipid phase
➢Timing	➢ Phase ratio
➢Equipments ▪ *Mechanical stirrers* ▪ *Homogenizers* ▪ *Colloid mills*	➢ Selection of emullgents

Methods of emulsion preparation [2]

Emulsion preparation proceeds by two steps:

✓Preparing primary emulsion

✓Diluting primary emulsion to make final volume

- Primary emulsion is prepared by mixing fixed ratio of oil, water & emullgent
- Selection of mixing procedure depends on type of emulsion preparation methods
  - ➢Continental or dry gum method
  - ➢English or wet gum method

Type of oil	Examples	Relative parts of components of primary emulsion		
		Oil	Water	gum
Fixed oil	➢Arachis oil ➢Castor oil ➢Cod-liver oil ➢Almond oil	4	2	1
Mineral oil	Liquid paraffin	3	2	1
Volatile oil	Turpentine oil Cinnamon oil Peppermint oil	2	2	1
Oleo-resin	Male ferns extract	1	2	1

Dry gum method

1. Mix accurately measured gum & oil in flat-bottomed mortar with pestle to make dispersion
2. After dispersion is completed, immediately add all measured amount of water at once with continuous unidirectional mixing to form 1° emulsion.
3. Continue mixing to get sustained cracking sound
4. Dissolve other remaining ingredients in oil or water depending on their polarity; then mix the resulting solution(s) with 1° emulsion
5. Transfer contents to graduated measuring cylinder or to calibrated final container
6. Adjust the volume with rinse water and then cap
7. Label the finished product

Note: In wet gum method, mucilage is formed by mixing gum with water, then it is blended with portion of oil

Example

- If a private prescription for internal emulsion is stated as follow, prepare emulsion emulsified with acacia

Rx

Ingredients	Amount [ml]
Arachis oil	52
Peppermint emulsion, concentrated	5.2
Chloroform water, double strength	104
Water QS, ad to	208

- Determine amount of each ingredients for 1° emulsion, on the basis of 4:2:1 ratio as the oil is fixed oil & use previously stated procedure for dry gum method

Ingredients of primary emulsion	Amounts of ingredients
Arachis oil	52 ml
water	26 ml
Acacia powder	13 gm

- Conduct dilution process to prepare 208 ml of emulsion

Example-2:

- Prepare liquid petrolatum emulsion[mineral oil emulsion] to be employed as lubricating cathartic using acacia & dry gum method

Ingredients for emulsion[mineral oil emulsion	Amount
Mineral oil	500 ml
Syrup	100 ml
Vanillin	40 mg
Alcohol	60 ml
Purified water, QS	1000 ml

8.7. Preservation of emulsions

- Required to resist microbial attack

Reason:

Microbial attack:

  - affect physicochemical properties of the formulation, causing color, odor, or pH changes and even phase separation
  - Triggers a health hazard

- W/o emulsions are less labile to attack than o/w ones
- Preservatives are not used in parenteral emulsions, which are sterilized by autoclaving or by using sterile components and aseptically assembling the final emulsion

Criteria for selection of effective preservative

- Must have **wide spectrum of activity** against bacteria, yeasts, and molds
- Should be free from toxic, irritant, or sensitizing activity
- Must have **adequate oil/water partitioning** with high percentage of unionized form in water phase

Antioxidants and Humectants

- **Antioxidants** are added to many pharmaceutical preparations to prevent oxidative deterioration on storage of the oil, emulsifier, or the drug itself. Such deterioration & destabilization of the formulation imparts unpleasant odor or taste

Example: BHA and BHT can be used at concentrations up to 0.2%, and the alkyl gallates.

- **Humectants** are often added to dermatological emulsion to reduce evaporation of water from emulsion during storage and use.

Example: propylene glycol, glycerol, sorbitol (5%),etc

8.8. Rheological properties of emulsions[RPE]

- Most emulsions display both plastic & pseudoplastic flow behaviour rather than simple Newtonian flow
- The pourability, spreadability &Syringeability of emulsion are directly determined by its rheological properties
- **RPE** is influenced by a number of interacting factors :
  - Nature of the continuous phase
  - Phase volume ratio
  - Particle [globule] size distributions

8.9. Physical stability of emulsion

Stable emulsion : an emulsion in which the globules retain their initial character and remain uniformly distributed throughout the continuous phase.

- There should be no phase changes or microbial contamination on storage, and the emulsion should maintain elegance with respect to odor, color, and consistency.

Examples of physical instability of emulsion

- Flocculation
- Creaming

Reversible physical instability

- Coalescence
- Cracking
- Phase separation

Irreversible physical instability

Note: Flocculation &/or creaming is/are generally regarded as a precursor to the irreversible process of coalescence

Chemical instabilities of emulsion

- **Rancidity** in natural oils due to oxidation by oxygen
- **Depolymerisation** of macromolecular emulsifiers by hydrolysis
- **Microbial degradation of emulgent**
- **Chemical instabilities** involving interactions b/n drug and emulsion excipients or b/n excipients themselves may lead to **physical instabilities**

Example:

Interactions between phenolic preservatives and polyoxyethylene non-ionic emulsifiers may lead to loss of emulsifying power & poor preservation

Any agent that destroys interfacial film leads to emulsion instability which can be chemical &/or physical in origin

1. Addition of agent incompatible with emullgent

Examples: SAAs of opposite ionic charge in emulsion

- Addition of Cetrimide (cationic) to an emulsion stabilized with sodium oleate (anionic)
- Addition of neomycin sulphate (cationic) to aqueous cream emulsified with anionic SAA
- Addition of electrolytes such as magnesium & calcium salts to emulsion stabilized with anionic SAA

2. **Bacterial growth**: Protein materials and non-ionic SAAs are excellent media for bacterial growth
3. **Temperature change**
   - Protein emulsifying agents may be denatured & the solubility characteristics of non-ionic emulsifying agents change with a rise in temperature above 70°C destroys most emulsions.
   - Freezing will also crack emulsion due to the ice formed disrupting interfacial film around droplets
4. **Flocculation** due to interaction of attractive forces or
5. **Deflocculation** due to repulsive forces
6. **Phase inversion**: O/W to W/O or vice versa
7. **Creaming**: due to density d/ce in the two phases

- Factors that influence rate of creaming of globules from emulsion & sedimentation rate of suspension particles are indicated by **Stokes' law**, as follows:

$$V = 2r^2g[\sigma-\rho]/9\eta$$

Where,

- **v** is velocity of creaming
- **r** is globule radius
- **σ** is density of dispersed phase
- **ρ** is density of dispersion medium
- **η** is viscosity of dispersion medium

8.10. Evaluation of stability of emulsion

- Assessments of relative stabilities of a series of emulsions may be obtained from estimations of the degree of separation of disperse phases as a distinct layer [cracking], or from the degree of creaming.
- More precise method for assessing emulsion stability is to follow the globule size distribution with time. An emulsion approaching the unstable state is characterized by the appearance of large globules as a result of the coalescence of others

Note: Separation of emulsion into two layers, i.e. cracking or breaking, indicates gross instability

Micro-emulsion formulations

Microemulsions

- Can be dispersions of oil droplets in water (o/w) or water droplets in oil (w/o) with mean globular diameter of **5–140 nm**
- Form spontaneously when components are mixed in the appropriate ratios
- Consist of apparently homogeneous transparent systems of low viscosity which contain a high percentage of both oil and water and high concentrations (15–25%) of emulsifier mixture
- Thermodynamically stable [very low interfacial tension]

Unit 9. Suspensions

9.1. Desirable properties
9.2. Sedimentation in suspensions
9.3. Interfacial properties of suspended particles
9.4. Electrical properties of suspended particles (EDL and DLVO theory)
9.5. Flocculated/deflocculated suspensions (properties and evaluations)
9.6. Formulation approaches (structure vehicle, controlled flocculation & combination)
9.7. Rheology of suspension
9.8. Preparation of suspensions (diffusible, indiffusible, poorly wettable solids)
9.9. Label and storage

9.1. Introduction

Pharmaceutical suspension

- Disperse system where internal phase is dispersed uniformly by agitation throughout external phase [suspending medium or vehicle] **or**
- Dispersions of an insoluble drug or other substance [suspensoids] in an aqueous or nonaqueous continuous phase **or**
- Coarse dispersion in which insoluble particles, generally greater than 1 μm in diameter, are dispersed in a liquid medium, usually aqueous **or**
- Liquid dosage form employed to deliver insoluble or poorly aqueous soluble drug to the patient

- Has internal phase:
  - ✓ consisting of a homogeneous or heterogeneous distribution of solid particles that have a specific size range & separate upon storage
  - ✓ maintained uniformly throughout suspending vehicle with the aid of a single or a particular combination of suspending agent(s)
- Thus ,the formulator targets controlling process of separation & optimising formulation stability
- Considered stable if, after agitation (shaking), the drug particles are homogeneously dispersed for a sufficient time to ensure that an accurate dose is removed for administration to the patient

9.2. Desirable properties of pharmaceutical suspension

- Must remain sufficiently homogenous for at least the period b/n shaking container & removing the dose [Low sedimentation rate]
- Sediment produced on storage, if any, must be easily resuspended by moderate container agitation [Redispersibility]
- Must not be too viscous to pour freely from the bottle or to flow through a syringe needle [Flowability]
- Any suspended particles should be small & uniformly sized in order to give a smooth, elegant product, free from a gritty texture [Aesthetically pleasing]

Types of pharmaceutical suspensions based on:

A. particles size

- ❖Colloidal suspension [particle size < 1μm]
- ❖Coarse suspension[particle size > 1μm]

B. diffusibility

- Diffusible suspensions
- Indifussible suspensions

C. route of administration

- ➢Oral suspension [Mixture]
- ➢Topical suspension[Lotion]
- ➢Parenteral suspension [injectable suspension]

Diffusible suspensions

Suspensions containing **light ,insoluble, or only very slightly soluble powders** in the vehicle, but which on shaking disperse evenly throughout the vehicle for long enough to allow an accurate dose to be poured

Indiffusible suspensions

Suspensions containing **heavy insoluble powders** in the vehicle and which on shaking do not disperse evenly throughout the vehicle long enough to allow an accurate dose to be poured

Note:

The preparation of indifussible suspensions involves **increasing viscosity of the vehicle using thickening agent / suspending agent** so that rate of settling of heavy insoluble powders will be delayed for reasonable time that permit dose measurement & administration

Oral suspension

- Oral liquids containing one or more insoluble active ingredients suspended in a suitable vehicle
- Suspended solids may slowly separate on standing but are easily redispersed
- Patients may have difficulty in swallowing solid dosage forms ,thus require drug dispersed in a liquid
- Some drugs that are used for adsorption of toxins, or to neutralize excess acidity are required to be present in the gastrointestinal tract in a finely divided form such that they provide high adsorptive surface area

Example: kaolin, $MgCO_3$ and magnesium trisilicate

- Taste of most drugs is more noticeable in solution rather than in suspension ,hence preferably prepared in suspension form

Example:

- Paediatric Paracetamol Oral suspension and CAF palmitate oral suspension are more palatable than their corresponding oral solutions

Parentral suspension

- Heterogeneous systems containing dispersed phase & dispersion medium
- Can be aqueous or nonaqueous
- Should be sterile, pyrogen-free, isotonic, & non-irritating
- Administered via subcutaneous or intramuscular route due to micronized particles size
- Should be resuspendable, syringeable,& injectable
- Syringeability and injectability are closely related.

Syringeability

- Ability of parenteral suspension to pass from storage vial easily through a hypodermic needle to injection site
- Ease of withdrawal, tendency for clogging and foaming, and accuracy of dose measurements

Injectability

- Performance of suspension during injection, involving pressure or force required for injection, evenness of flow, aspiration qualities, and tendency of clogging should be optimized

- Both injectability & Syringeability are diminished with increased viscosity, density, particle size, and solids concentration
- Clogging of needle may occur due to blockage by a particle or by bridging effect of multiple particles

Note: Individual particle size should not be greater than one-third of the needle's internal diameter

Requirements for parentral suspension preparation

1. Microbiological control
2. Excipients allowance
3. Mechanical flow properties

Excipients for parentral suspension

- Nonpyrogenic, nontoxic, & chemically inert

Examples:

- **Wetting /flocculating agents**: impart stability & mechanical flow properties
- **Suspending agents**
- Aqueous [WFI] or nonaqueous [PEG,glycerin, ethanol, etc] **vehicles** can be used depending on nature of the drug
- Microbiological control can be achieved via sterilization or aseptic production technique

Advantages of pharmaceutical suspensions

- Mask taste of therapeutic agents with bitter taste
- Employed to administer insoluble drugs in their liquid state to patients who have difficulty swallowing solid-dosage forms
- Formulated to provide controlled drug delivery

  e.g. as intramuscular injections
- Useful for poorly water soluble drug delivery
- Absorption will be quicker than solid dosage forms

Note: Dissolution of low-solubility drug is possible using large solvent volume or co-solvent, however dilution & precipitation ,respectively remain problems

Disadvantages of pharmaceutical suspensions

- Fundamentally they are unstable
- Requires shaking before use
- Accuracy of dose is less than with equivalent solution
- Developing aesthetic suspension formulations is difficult
- May bulky & therefore difficult for a patient to carry

Quiz-1

1. Preparing sparingly water soluble drug using a liquid system containing alcohol in water helps to produce stable:

   A] solution. Du you agree? Why?

   B] suspension . Du you agree? Why?

2. Abebe, a potential pharmacist, suggested that drug with unpalatable taste should be prepared in solution, not in suspension since such taste masking is easy in the former preparation. Du you agree ? Why?

9.3. Sedimentation in suspension

Coarse suspensions sediment at faster rate than colloidal suspension under the influence of gravity as shown by Stoke's law: $U = d^2 (\rho_s - \rho_l) g/18\eta$

Where U=average settling velocity of particles

d =mean diameter of the particles

ρ_s = density of solid particles

ρ_l = density of fluid phase

η = viscosity of fluid phase

g = acceleration due to gravity

Discuss effect of each variables on particle settling rate

What is the effect of suspending agent on settling rate? Why?

Suspending agent /Thickening agent

Suspending agents commonly used in pharmaceutical suspensions include:

- **Cellulosics**: sodium carboxymethylcellulose, microcrystalline cellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, starch, sodium starch glycolate, and powdered cellulose
- **Clays**: attapulgite, bentonite, magnesium aluminum silicate, kaolin, silicon dioxides
- **Gums**: acacia, agar, algins, pectin, tragacanth
- **Polymers**: carbomers, polyvinyl alcohol, povidone, polyethylene oxide

Ideal suspending agent should:

- Be readily and uniformly incorporated in formulation
- Be readily dissolved or dispersed in water without resort to special techniques
- Ensure formation of loosely packed uncaked system
- Not influence drug dissolution or absorption rate
- Be inert, nontoxic and free from incompatibilities

Electrical properties of dispersed particles

- Following dispersion within an aqueous medium, particles may acquire a charge. **How?**
  - By ion dissolution
  - By ionisation of functional groups on drug molecule
  - Ions adsorption on to particle surface

Ion dissolution

- Surface charge of colloidal particle **is controlled by the charge of ion** present in excess in the medium

Examples; $AgNo_3$ + Excess NaI → AgI +$NaNo_3$ + excess iodide ions

- Silver iodide in a solution with excess iodide Particles acquire negative charge
- Aluminum hydroxide in a solution with excess hydroxide impart negative charge on particles surface
- **Potential determining ions:** ions whose concentration determine electric potential at the particle surface (e.g. Ag^+ , I^-, H^+, OH^-)

Ionisation of functional groups

- Insoluble drug particles may possess such ionisable functional groups as -COOH or -NH_2 on their molecules
- Dissociation of acidic groups on particle surface give rise to a negatively charged surface. Conversely, a basic surface will take on a positive charge.
- Degree of ionisation of such molecules depends on:
  - ➢ pK_a of the molecules [i.e., acidic or basic strengths of the surface groups] **and**
  - ➢ pH of the surrounding solution

- Surface charge of colloidal particle is controlled by ionization of surface groupings

Examples

A. Polystyrene latex has carboxylic acid group at the surface, ionize to give negatively charged particles

B. Acidic drugs as ibuprofen & nalidixic acid acquire surface negative charge

C. Amino acids & proteins have carboxyl & amino groups thus their ionization depend on pH:

NH_2COO^- ⟶ $NH_3^+COO^-$ ⟶ NH_3^+COOR

At high pH, alkaline medium, negatively charged

Zwitterion
Iso-electric point
Zero charge

At low pH, acidic medium, positively charged

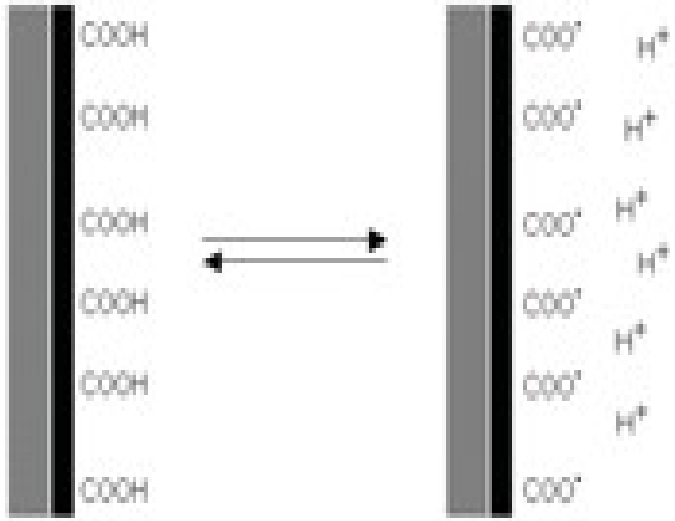
Iso-electric point

- pH at which +ve charges equal to -ve charges, i.e. net charge of the amino acid = zero.
- Definite pH specific for each protein [finger print]
- pH where protein is least soluble& precipitated

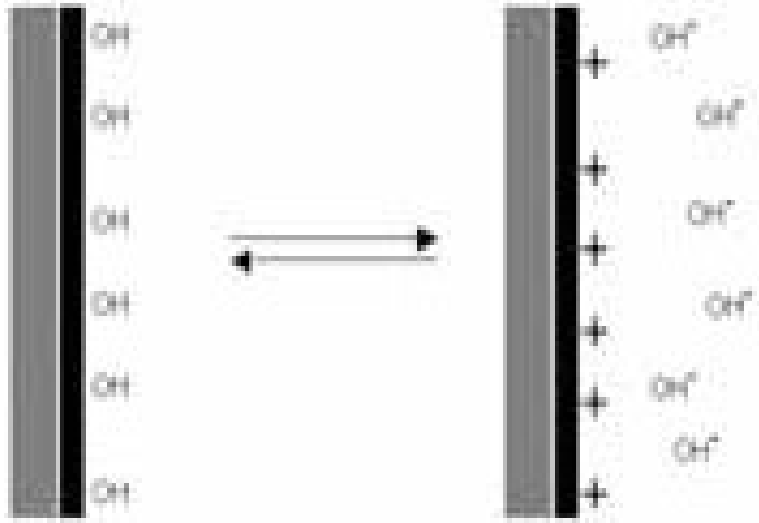
How can you precipitate insulin?

By adjusting pH of the solution to that of insulin iso-electric point (PH 5.2)

- Surface charge can be reduced to zero by suppressing surface ionisation. How?
- by decreasing pH for negatively charged particles **or**
- by increasing pH for positively charged particles



Origin of surface charge by ionisation of acidic groups to give a negatively charged surface



Origin of surface charge by ionisation of basic groups to give a positively charged surface

- Quiz-2
- Formation of insulin suspension at pH 5.2 is unthinkable. Do you agree or disagree? Why?

Adsorption of ions on to particle surface

- Surface charge of colloidal particle is controlled by unequal adsorption of oppositely charged ions
- Ions may be adsorbed on to particle surface from **aqueous solution** containing electrolytes, or

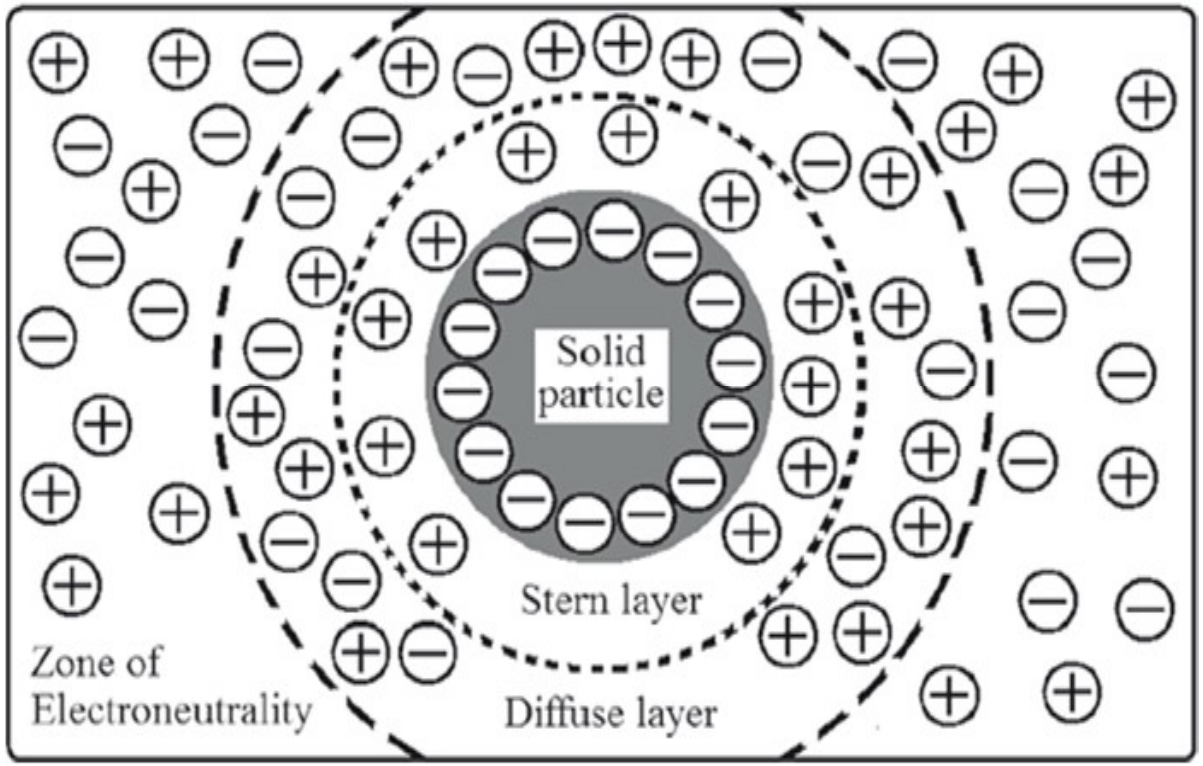
If no added electrolytes:

✓ OH^- preferentially adsorbed on to particle surface

✓ H_3O^+ ions, by contrast, are more hydrated than hydroxyl ions ,thus remaining within bulk medium

Note: Surfaces of solution in water are negatively charged than positively charged since cations are more hydrated than anions so cations reside in bulk while less hydrated anions adsorbed on surface

- Development of a net charge at particle surface affects distribution of ions in the surrounding interfacial region, resulting in an increased conc. of counter ions [ions of opposite charge to that of the particle] close to the surface, forming **electrical double layer** round each particle.


Solid particle
Stern layer
Zone of Electroneutrality
Diffuse layer

Qiz-3

- It is designed to produce a suspension of protenious drug whose iso-electic point pH is known to be 4.5. Suggest how to prepare.

Main features of electrical double layer

- Potential-determining ions :Ions responsible for Nernest potential
- Ions, e.g. cations, are adsorbed on to particle surface, leaving anions and remaining cations in solution.
- Adsorbed cations generates a potential called *Nernest potential* on particle surface
- Anions are then electrostatically attracted to (positive) surface of the particle. Thus, their presence will repel subsequent approach of further anions. This is referred to as the first section of the double layer & is therefore composed of adsorbed ions on the surface, counter-ions & bound hydrated solvent molecules.

- The boundary between the first and second layers of the electrical double layer is referred to as the *Stern plane.*

Features of the Stern plane

- the adsorbed ions on the surface of the particle
- the adsorbed counter-ions at the surface of the particle
- Stern plane falls through centre of counter-ion layer
- Normally, the charge at the surface of the particle is greater than charge at the Stern plane

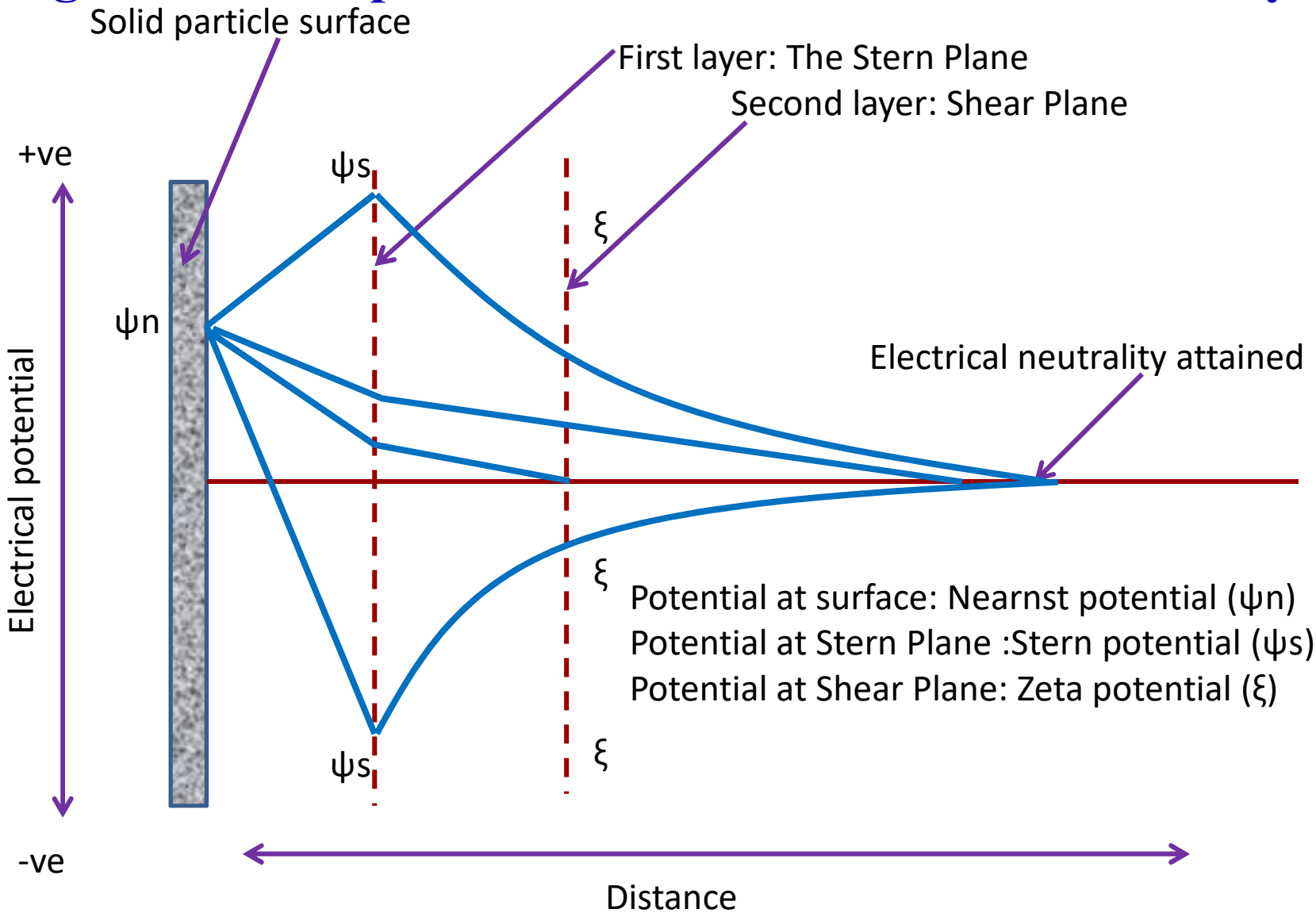
- The second layer contains predominantly hydrated counter-ions that are loosely attracted to the surface of the particle

Features of the second layer

- The boundary of this second layer will possess a potential, called **zeta potential** *whose* magnitude is generally less than the potential at the Stern plane
- If the particle is rotated, this second layer forms the shear plane, i.e. the effective surface.
- At a certain distance from the surface of the particle, electrical neutrality is restored

- **Interaction b/n suspended particles in a liquid medium** is related to distance of separation b/n the particles. In principle, three events are possible:
- **No interaction:** particles are maintained sufficiently distant from one another, no sedimentation thus remain thermodynamically stable.
- **Coagulation (agglomeration):** Particles form an intimate contact with each other [cake], producing pharmaceutically unacceptable formulation
- **Loose aggregation (floccules):** formed by loose reversible interaction b/n particles, thus redispersed upon shaking

Diagrammatic representation of the electrical double layer



9.6. Flocculation & deflocculation of Suspension

- Whether or not a suspension is deflocculated or flocculated depends on relative magnitudes of the forces of repulsion and attraction b/n particles
- Zeta potential is a measurable indication of apparent particles charges in dispersion medium
- Relatively high zeta value indicates that repulsive forces exceed attractive forces
- Accordingly, particles are individually dispersed forming deflocculated suspension

Flocculated suspension systems

- Repulsive barriers have been reduced
- Particles settle as flocs , not as individual particles
- Supernatant rapidly appear clear after sedimentation
- Particles form loosely bonded structures called flocs or flocculates, thus flocculation imparts a structure to the suspension with virtually no increase in viscosity
- Sediment is not closely packed & caking does not readily occur as particles arranged randomly in flocs

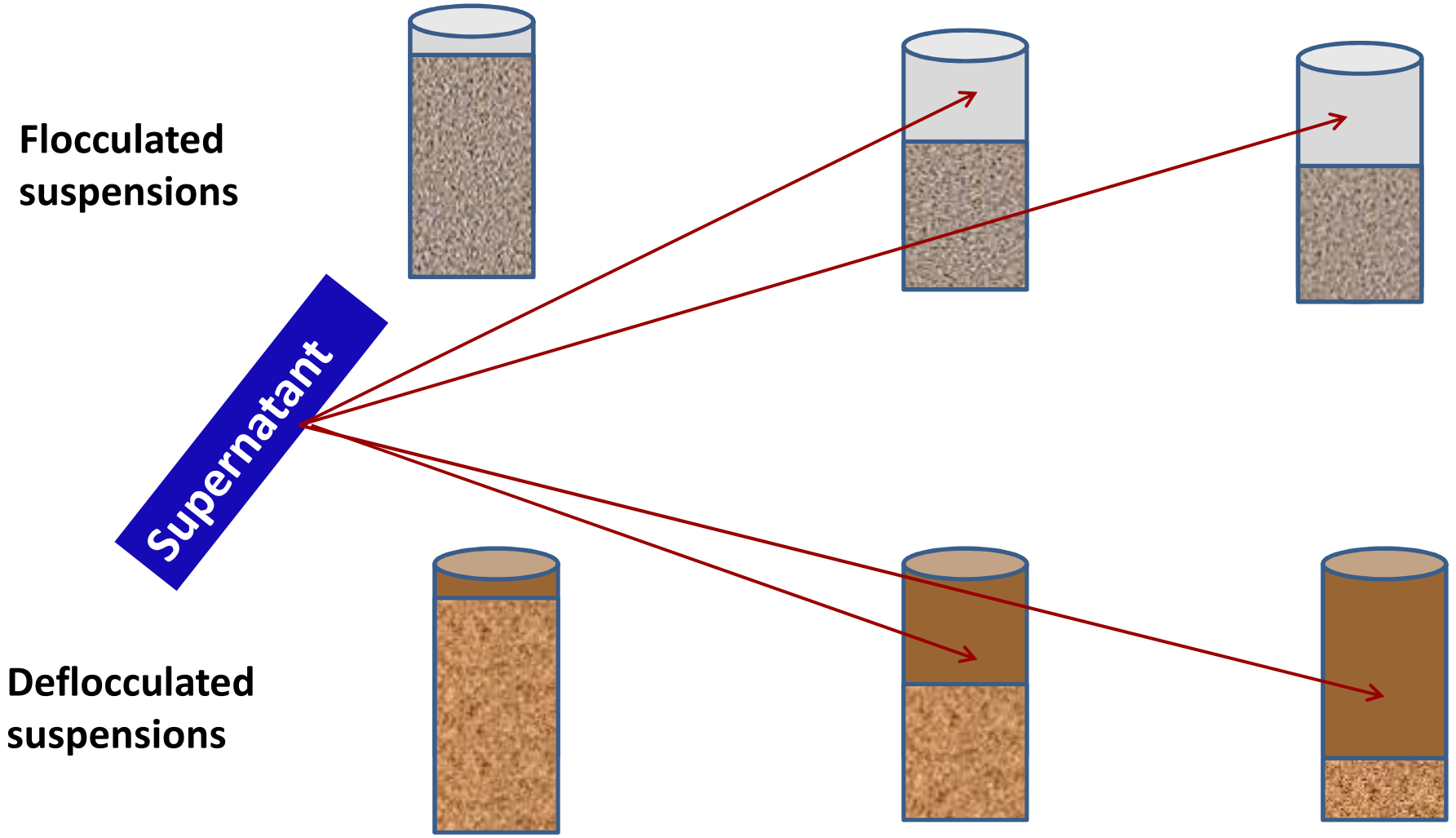
Aim of suspension formulation :to achieve partial or controlled flocculation

Deflocculated suspension systems

- Particles are not associated but remain as a discrete unit thus allowing slow settling as individuals not as flocs
- After shaking , supernatant remain cloudy due to slow settling of discrete particles
- Pressure on individual particles causes close packing of particles &irreversibly bounding together to form a cake

Note

- Caking is the most serious of all physical suspension stability; usually prevented by flocculating agent
- Caking cannot be eliminated by particle size reduction or by increasing viscosity of continuous phase



Sedimentation behaviour of flocculated & deflocculated suspensions

Summary

1. Deflocculated systems have the advantage of a slow sedimentation rate, thereby enabling measuring uniform dose from the container, but when settling does occur the sediment is compacted and difficult to redisperse
2. Deflocculated system with sufficiently high viscosity to prevent sedimentation would be an ideal formulation, however such viscosity challenges suspension flowability.

3. Deflocculation with high viscosity cannot guarantee, however, that the system would remain homogenous during the entire shelf-life of the product
4. **Under-flocculation** gives those undesirable properties associated with deflocculated systems
5. **Over-flocculated product** will look inelegant and, to minimize settling, the viscosity of the product may have to be so high that any necessary redispersion would be difficult

7. Usually compromise is reached in which suspension is partially flocculated to enable adequate redispersion if necessary, and viscosity is controlled so that the sedimentation rate is at a minimum
8. Flocculated systems form loose sediments that easily redisperse, but sedimentation rate is fast & hence there is a possibility of inaccurate dose measuring & administration ; also, the product will look inelegant
9. Both flocculated & deflocculated suspensions have their own short-comings.

Then, how to overcome this problem?

9.7. Suspension formulation approaches

Controlled flocculation

- Intentional formation of loose agglomerates of particles that held together by comparatively weak bonding forces
- Can be made by any approach that forms flocculated system by minimizing repulsive forces & improving attractive forces of particles
- Approaches to controlled flocculation:
  - ✓ particle size control
  - ✓addition of electrolytes
  - ✓addition of polymers

Flocculating agents

- Incorporation of non-ionic wetting agent forms deflocculated suspension

Reason

- Reduction in solid/liquid interfacial tension
- Hydrated hydrophilic layer around each particle form mechanical barrier to aggregation
- Use of ionic surfactant to wet the solid could produce either a flocculated or a deflocculated system, depending on any charge already present on the particles.

- If particles are of opposite charge to that of the surfactant then neutralization will occur
- If a high charge density is imparted to the suspended particles then deflocculation will be the result
- Conversion of suspension from a deflocculated to a partially flocculated state can be achieved by the addition of:
    - ➢electrolytes
    - ➢surfactants &/or
    - ➢hydrophilic polymers

Electrolytes

Addition of optimal amount of inorganic electrolyte to aqueous suspension reasonably lower zeta potential of dispersed particles , forming flocculated suspension

- Ability of electrolyte to flocculate hydrophobic particles depends on the valency of its counter-ions
- Although trivalent ions are more efficient, they are less widely used than mono- or divalent electrolytes

Reason

- Generally more toxic than mono- or divalent electrolytes
- Trigger precipitation of hydrophilic polymers[usually negatively charged] included in suspension formulation

- Most widely used electrolytes include sodium salts of acetates, phosphates and citrates
- Concentration of electrolyte selected depends on the desired degree of flocculation
- Adding excessive electrolyte or charge results in the formation of reversal form of deflocculated system

Example-1: Dispersion of Bismuth subnitrate particles in water

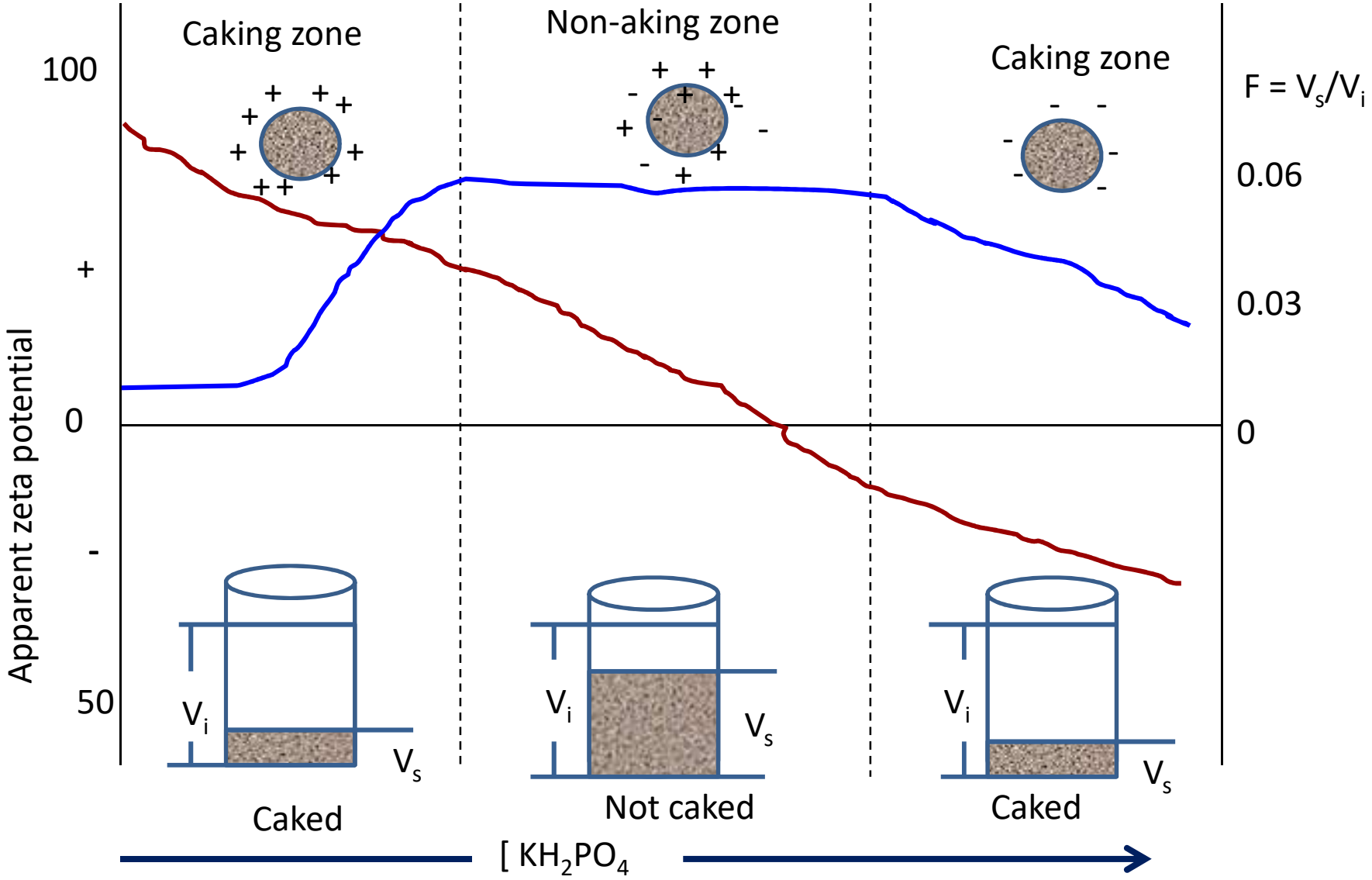
- Particles possess a large positive charge/zeta potential
- The system is peptized/deflocculated due to strong inter-particles repulsive forces
- Addition of monobasic potassium phosphate to Bismuth subnitrate suspension reduces zeta potential due to adsorption of negatively charged phosphate anions
- With the continuous addition of monobasic potassium phosphate zeta potential eventually falls to zero & then increase in negative direction occurs leading to reversal effect

- Microscopic examination reveals that at certain positive zeta potential , maximum flocculation occurs & persist until zeta potential become sufficiently negative for deflocculation to reoccur

Note: The onset of flocculation coincides with the maximum sedimentation volume[F]

- 'F' remains constant while flocculation persists
- 'F' starts to fall after the zeta potential is adequately negative to cause peptization
- No caking of sediment while flocculation persists correlating that 'F' is at its maximum & zeta potential is declining
- At maximum values of zeta potential,caking becomes apparent

Caking diagram showing flocculation of Bismuth subnitrate particles by flocculating agent :monobasic potassium phosphate



Example-2: Sulfamerazine aqueous suspension

- Zeta potential of sulfamerazine particles is negative
- Upon addition of $AlCl_3$, negative zeta potential progressively is declining due to adsorption of trivalent aluminium cations
- When adequate electrolyte is added, zeta potential reaches zero & the increase in positive direction

Plot a caking diagram for the above example

Surfactants

- Ionic surface-active agents may cause:
  - flocculation by neutralizing charge on each particle
  - deflocculation by imparting charges identical to that found on particles surfaces
- Non-ionic surfactants have negligible effect on particle charge density yet adsorbed on to more than one particle forming loose flocculated structure

Polymeric flocculating agents

- Linear branched-chain molecules
- Used to control flocculation

How ?

- Form a gel-like network within suspension system
- Adsorbed on to surfaces of dispersed particles, thus holding them in a flocculated state

Examples

- Starch, alginates, cellulose derivatives, tragacanth, carbomers and silicates

Factors affecting polymeric flocculating agents

1. Excessive blending

- Interferes cross-linking of adjacent particles
- Each molecule of a polymer adsorbed on to individual particles forming hydrophilic barrier around each particle that inhibit their aggregation
- Results in the formation of deflocculated system

2. High concentration of polymer

May coat whole surface of each particle preventing their aggregation & forcing them to behave independently so as to form deflocculated system

Wetting of particles & wetting agents

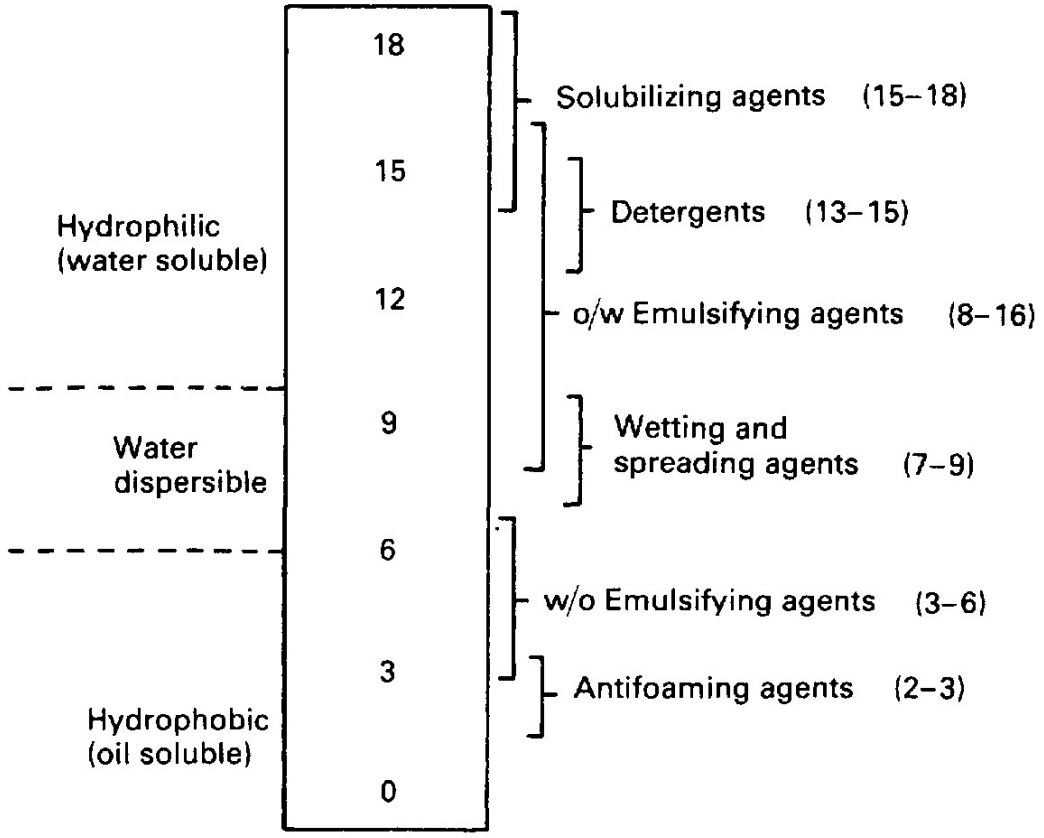
- Some insoluble solids may be easily wetted by water & disperse readily throughout aqueous phase with only minimal agitation while most exhibit varying degrees of hydrophobicity and not easily wetted
- To ensure adequate wetting, interfacial tension b/n solid & liquid must be reduced so that adsorbed air is displaced from the solid surfaces by the liquid.
- Particles will then disperse readily throughout the liquid, particularly if intense shearing action is used during mixing

Most widely used wetting agents

- Surface-active agents
- Hydrophilic colloids
- Solvents

Surface active agents [SAA or surfactants]

Classification of surface active agents based on HLB scale



HLB scale showing classification of surfactant function.

- SAA having HLB value 7 to 9, exclusive, can be used as wetting agents
- SAAs have both polar & non-polar moieties in their molecules
- Hydrocarbon chains are adsorbed by hydrophobic particle surfaces, whereas polar groups project into aqueous medium and become hydrated
- Wetting of solid occurs as a result of a fall both in interfacial tension b/n solid & liquid ;, to a lesser extent, b/n liquid and air
- Most surfactants are used as wetting agents at concentrations $\leq 0.1\%$

Examples of wetting agents

Wetting agents for oral use

- Polysorbates (Tweens)
- Sorbitan esters (Spans)

Wetting agents for external application

- Sodium lauryl sulphate
- Sodium dioctylsulphosuccinate
- Quillaia extract

Wetting agents for parenteral administration

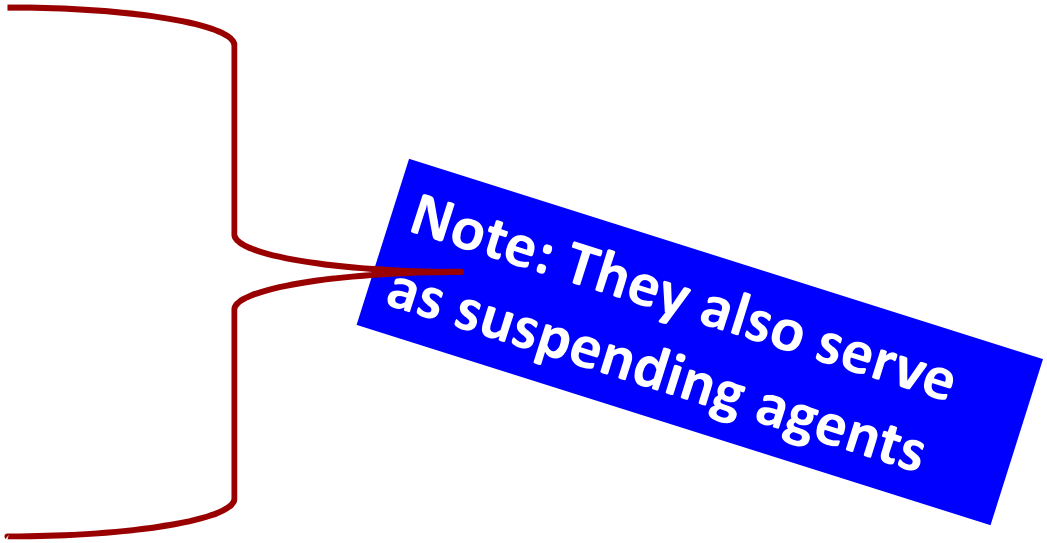
- Polysorbates
- Poloxamers [polyoxyethylene/polyoxypropylene copolymers] and lecithin

Hydrophilic colloids

- Behave as protective colloids by coating solid hydrophobic particles with a multi-molecular layer
- The layers promote wetting by imparting a hydrophilic character to insoluble solid particles

Examples

- Acacia
- Bentonite
- Tragacanth
- Alginates
- Cellulose derivatives



Solvents

- Water miscible solvents reduce liquid/air interfacial tension
- Solvent penetrates loose agglomerates of powder displacing air from pores of individual particles, so enabling wetting to occur by dispersion medium

Examples

- ❖ Alcohol
- ❖ Glycerol
- ❖ Glycols

9.8. Rheology of suspensions

Rheology: the study of flow & deformation properties of matter

- Proper understanding of rheological properties of pharmaceuticals is essential to the preparation, development, evaluation & performance of suspension
- Rheological properties of suspensions are markedly affected by the degree of flocculation

Reasons

- Amount of free continuous phase is reduced, as it is entrapped in the diffuse floccules
- Consequently, apparent viscosity of a flocculated suspension is normally higher than but deflocculated one
- In addition, in a highly flocculated disperse system structured systems result due to possibility of interaction b/n floccules

Characteristics of ideal pharmaceutical suspension

At low rates of shear

- Exhibit high apparent viscosity
- On storage, suspended particles either settle very slowly or, preferably, remain permanently suspended

At higher rates of shear [moderate shaking]:

- Apparent viscosity falls sufficiently
- Product is poured easily from its container

Topical suspension

- Should spread easily without excessive dragging, but should not be so fluid that it runs off skin surface

Parenteral suspension

- Should pass easily through a hypodermic needle with only moderate pressure applied to syringe plunger

Note:

Maintaining adequate flowability & syringability necessitate modification of initial high apparent viscosity of suspension using viscosity modifiers

Mentioned below

Polysaccharides such as Tragacanth, Accacia, Na-alginate

Water-soluble celluloses : Disperse in water to produce viscous colloidal solutions to be used as suspending agents

Examples:

Methylcellulose, Hydroxyethylcellulose, Carmellose sodium (sodium carboxymethylcellulose)

Hydrated silicates such as bentonite & magnesium aluminium silicate

- Have useful suspending properties since they hydrate readily, absorbing up to 12 times their weight of water, at elevated temperatures thus forming thixotropic gels

9.9. Preparation of suspension [diffusible, indiffusable, poorly wettable solids] ???

- Suspension can be prepared by different methods such as dispersion method or Precipitation method
- Before commencing with suspension preparation suitable formulation ingredients should be identified
- Optimal particle size ranges along with wetting & suspending agents should be established
- Pestle & mortal , bottles & caps , labels / leaflets are needed

9.10. Physical stability of pharmaceutical suspension

- Defined as the condition in which particles do not aggregate but remain uniformly distributed throughout the dispersion medium [ideal hence seldom realized]
- Defined as the condition in which particles may aggregate & easily resuspended by a moderate amount of agitation & then remain uniformly distributed throughout the dispersion medium for adequate time that allow accurate dose measuring & administration [Practical or real]

Thermodynamically stable disperse system , where there is no interaction between particles , may be physically unstable

Reason:

Particles in a suspension sediment under influence of gravity

They settle at the bottom of container, larger particles reaching the bottom initially & smaller particles occupying the space between the larger particles, forming reversible sediment [flocs] or irreversible sediment[Cake]

- In flocculated systems, rate of sedimentation of flocs is high & volume of sediment produced is large due to large void volume within floccules structure
- Ability to undergo flocculation will increase as concentration of suspended particles increases, due to greater probability of particle–particle interactions
- Caking due to sedimentation can be controlled by establishing optimal particle size, viscosity of dispersion medium & density difference based on Stoke's law
- Set optimal particle size range & viscosity by milling & adding hydrophilic poymers ,respectively

9.11. Assessment of sedimentation of pharmaceutical suspensions

Usually performed by measuring:

- sedimentation volume[F]

and/or

- degree of flocculation [β]

Sedimentation volume[F] :

- ❖ Assessed using simple ,inexpensive graduated measuring cylinder [100-1000 ml]
- ❖ It is the ratio of the volume of sediment (Vs) to the initial volume of suspension,(Vi): $F = V_s/V_i$
- ‘F’ may range <1 to values ≥ 1

Reason

- ‘F’ of deflocculated & flocculated suspensions are < 1 & ≥ 1,respectively since flocculated structure occupy relatively large volume due to large inter-floccules void space & deflocculated particles form cake

Note: The greater the value of ‘F’, the more stable the suspension and When F = 1, no sedimentation or caking

Degree of flocculation (β)

- Ratio of ultimate sedimentation volume of flocculated suspension [$\mathbf{F_f}$] to ultimate sedimentation volume of deflocculated suspension [$\mathbf{F_\infty}$]
- preferred measurement as it provides a point of reference, i.e. the suspension before and after flocculation

$$\beta = F_f / F_\infty$$

- As value of β is approaching unity, degree of flocculation decreases

Quiz:

- Deflocculated & flocculated suspensions are pharmaceutically acceptable types of suspensions. Do you agree? Why?

10. COLLOIDS

10.1. Introduction

10.2.Types of colloids

10.3. Electrical properties of colloids

10.4. Pharmaceutical application of colloids

10.1 Introduction

- The term colloid applies broadly to systems containing at least two components, in any state of matter, one dispersed in the other, in which the dispersed component consists of large molecules or small particles
- Molecular or particle sizes of colloids vary in the range 1nm to 1 μm

Biological & pharmaceutical significance of colloids

- Many biological structures are colloidal in nature
  - ✓blood [dispersion of corpuscles in serum]
  - ✓bone [a dispersion of $Ca_3(PO_4)_2$in collagen]
- Medical application of colloids
  - o Diagnostic imaging [radiolabeled, parenterally administered colloids]
  - o Adjuvant to improve therapy [Adsorption of toxins onto a colloidal carrier to enhance immune effect]

- Drug preparation (colloidal silver protein an effective germicide)
- Preparation of dosage forms
- Colloid drug delivery systems [nano-particle ,liposome , microspheres & macromolecular drug complexes)
- Drug targeting, controlled release, and protection of the drug substance
- Colloid drug-delivery systems [topically, orally, parenterally and by inhalation]

10.2 Types of colloids: [Three]

Classification is made based on interaction of dispersion phase with dispersion medium

1. Lyophilic colloids
2. Lyophobic colloids
3. Association colloids

Lyophilic colloids

- Thermodynamically true solutions, thus best treated as a single phase system
- Lyophilic colloidal solutions are thermodynamically stable & form spontaneously when solutes interact with solvent
- Strong interaction b/n solute & solvent supplies sufficient energy to break up the disperse phase

Lyophobic colloids

- Thermodynamically unstable & have a tendency to aggregate due to poor dispersed phase–dispersion medium interactions
- Aggregatively unstable ,hence remain dispersed in a medium only if the surface is treated to cause a strong repulsion between particles
- However, treated colloids are thermodynamically unstable but kinetically stable since aggregation can be prevented for long periods

Association colloids

- Dispersed phase molecules are soluble in continuous phase & spontaneously "self-assemble" or "associate" to form aggregates in colloidal size range

Example:

- Aggregates or "associations" of amphipathic surface active molecules

  Amphipathic SAA

  ✓Soluble in the solvent

  ✓their molecular dimensions < colloidal size range

  ✓Concentrations above CMC in a solution form association colloids (micelles)

Amphipathic molecules

- consist of two parts: lyophilic & lyophobic portions
- tend to adsorb at interfaces to reduce the interfacial energy b/n lyophobic portion of the molecule & the medium
- On micellization, lyophobic portions of surfactant molecules associate to form regions from which the solvent is excluded, while the lyophilic portions of the molecules remain on the outer surface
- Micelle formation is spontaneous, depending on the lyophilic–lyophobic balance of the SAA, concentration of SAA, and temperature of the system

10.3. Properties of colloids

A. Optical properties

B. Kinetic properties

C. Electrical properties

A. Optical properties of colloids

Light scattering

- When a beam of light is passed through a colloidal solution some of the light may be absorbed producing coloured sol ,some is scattered and the remainder is transmitted undisturbed through the sample. Because of the scattered light the sol appears turbid: this is known as the **Tyndall effect**
- Light scattering measurements are of great value for estimating particle size, shape and interactions, particularly of dissolved macromolecular materials, as the turbidity depends on the size (molecular weight) of the colloidal material involved.

- Light-scattering measurements are particularly suitable for finding size of micelles of SAA and for the study of proteins and natural and synthetic polymers

Optical microscope never visualize colloidal particles

Electron microscopy

- Capable of giving actual pictures of dried particles
- Used to observe size, shape & structure of colloidal particles owing to its high resolving power
- Gives no information on solvation or configuration in solution, a problem solved using ESEM
- **Environmental scanning electron microscopy[**ESSEM] allows the observation of material in the wet state

Ultramicroscope is used in micro-electrophoresis for measuring particle charge

B. Kinetic properties of colloids

- Refers to properties of colloidal systems in relation to motion of particles with respect to dispersion medium
- Measurement of these properties enables molecular weight or particle size determination
- **Thermal motion** manifests itself as Brownian motion, diffusion and osmosis
- **Gravity** (centrifugal field) leads to sedimentation
- **Viscous flow** is due to externally applied force

Brownian motion

- Irregular & complicated zigzag path formed by colloidal particles due to their random collisions with the molecules of the dispersion medium
- **Diffusion** Owing to Brownian motion, colloidal particles spontaneously diffuse from region of higher concentration to lower concentration The rate of diffusion is expressed by Fick's first law: $\frac{dm}{dt} = -DAdC/dx$

where *dm*=mass of substance diffusing in time *dt* across an area *A* under the influence of a conc. gradient *dC/dx* (the minus sign denotes that diffusion takes place in the direction of decreasing conc.). *D* is diffusion coefficient with dimensions area per unit time.

Sedimentation

- Consider a spherical particle of radius ‘a’ and density ‘σ’ falling in a liquid of density ‘ρ’ and viscosity ‘η’ where ‘g’ is acceleration due to gravity
- Velocity v of sedimentation is given by Stokes' law:

$$V = 2a2g(\sigma - \rho)/9\eta$$

- If the particles are subjected only to the force of gravity, then as a result of Brownian motion, the lower size limit of particles obeying Stokes' law is about 0.5 μm.
- A stronger force than gravity is therefore needed for colloidal particles to sediment
- Thus, high-speed centrifuge termed ultracentrifuge, which can produce a force of about 1*06g is used.*
- In a centrifuge, g is replaced by **$\omega^2 x$,** *where ω is* the angular velocity and *x the distance of the particle* from the centre of rotation,then Stoke,s law becomes:

$$V = 2x(aw)^2(\sigma - \rho)/9\eta$$

C. Electrical properties of colloids

- Most surfaces gain a surface electric charge when brought into contact with an aqueous medium
- Principal charging mechanisms of colloids:
  - ❖Ion dissolution
  - ❖Ionization
  - ❖Ion adsorption
  - ❖Electrical double layer

- **Unequal dissolution** of the oppositely charged ions impart surface charge to particles
- Example, the particles of silver iodide in a solution with excess [I^-] will carry a negative charge, but the charge will be positive if excess [Ag+] is present.
- Ag+ and I^- are **potential determining ions** since they determine electric potential at particle surface

Ionization

The charge is controlled by ionization of surface groupings such as carboxylic acid or amino group

Examples:

- Carboxylic acid groupings of polystyrene latex, ibuprofen and nalidixic ionize to give negatively charged particles
- Amino acids & proteins acquire their charge mainly through the ionization of carboxyl and amino groups to give COO- and $NH3^+$ ions

Note: Erythrocytes & bacteria usually acquire their charge by ionization of surface chemical groups such as sialic acid.

Ion adsorption

A net surface charge can be acquired by the **unequal adsorption of oppositely charged ions**.

Surfaces in water are more often negatively charged than positively charged, because cations are generally more hydrated than anions. Example:

- Consequently, cations have the greater tendency to reside in the bulk aqueous medium, whereas the smaller, less hydrated and more polarizing anions have a greater tendency to reside at the particle surface
- **Surface-active agents** are strongly adsorbed and have a pronounced influence on the surface charge, imparting either a positive or negative charge depending on their ionic character.

The electrical double layer

- Consider a solid charged surface in contact with an aqueous solution containing positive and negative ions
- Surface charge influences distribution of ions in the aqueous medium; ions of opposite charge to that of the surface, termed counter-ions, are attracted towards the surface; ions of like charge, termed co-ions, are repelled away from the surface
- However, thermal agitation will also affect distribution of ions by redispersion of ions in solution
- Result : Formation of electrical double layer, made up of charged surface and a neutralizing excess of counter-ions over co-ions (the system must be electrically neutral) distributed in a diffuse manner in the aqueous medium

10.4. Pharmaceutical applications of colloids

Uses of colloid drug-delivery systems:

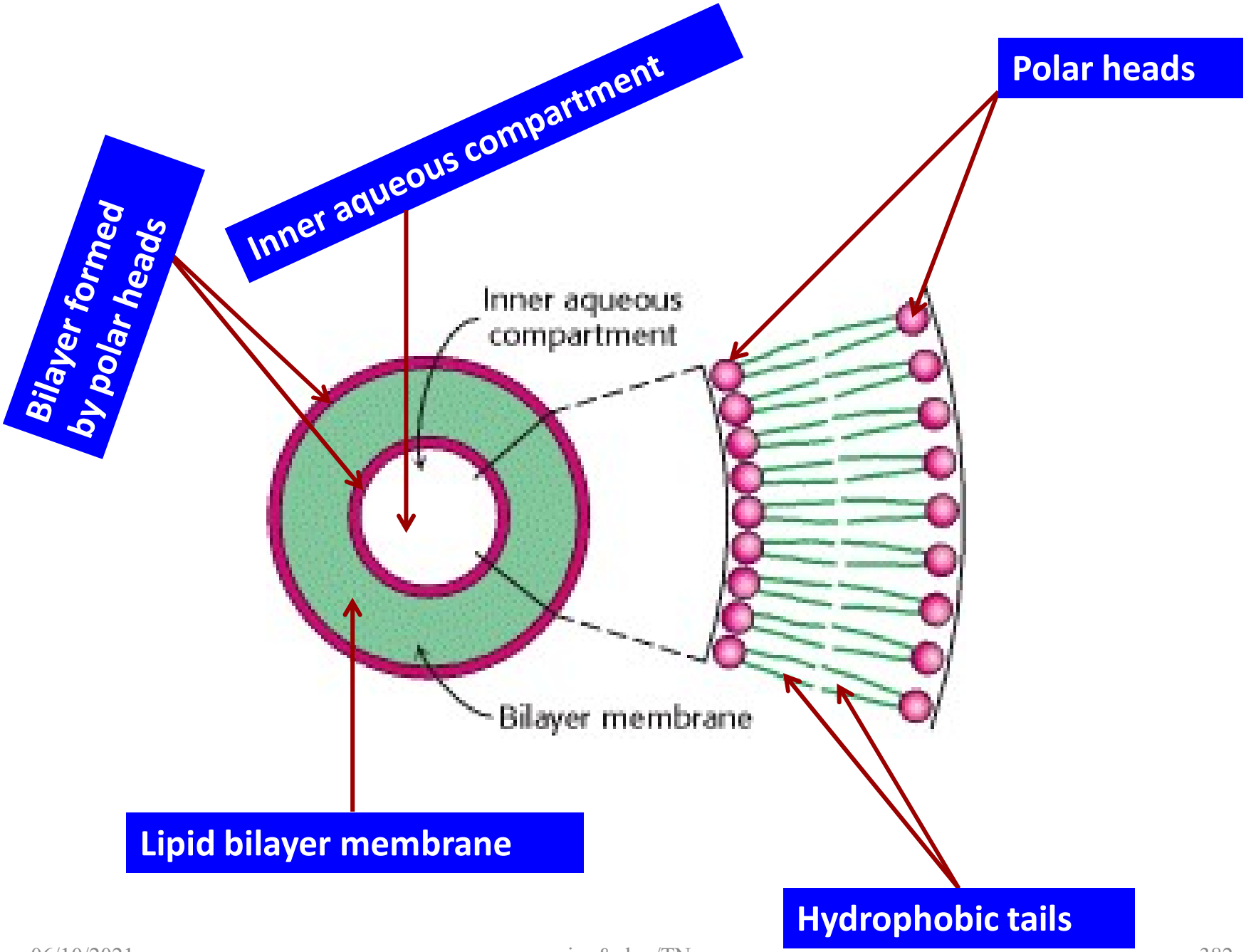
- Increase the bioavailability of drug substances
- Improve drug stability,
- Sustain and control drug-release rates
- Target drugs to specific sites in the body
- Stimulate the immune system

Colloids that have pharmaceutical application:

- Liposomes
- Microspheres
- Nanoparticles
- Micells
- Microemulsion
- Hydrogels
- Nanocrystals

Liposomes

- Artificial lipid vesicles consisting of one or more lipid bilayers enclosing a similar number of aqueous compartments for polar drug entrapments
- Used to deliver both polar & non-polar drugs to their target
- Liposomes are unstable, have low carrying capacities, & tend to be "leaky" to entrapped drug substances
- Incorporation of such molecules as cholesterol, cetylphosphate, & stearylamine into phospholipid bilayer can alter properties of liposomes
- Presence of cholesterol results in a more stable, less "leaky" membrane


Bilayer formed by polar heads
Inner aqueous compartment
Polar heads
Inner aqueous compartment
Bilayer membrane
Lipid bilayer membrane
Hydrophobic tails

- Polymerized liposomes having phospholipids with polymerizable moieties are more stable and less ‘leaky.’’
- Immunoglobulins , attached to surface of liposomes, enables actively targeting them to specific sites.
- Polyethylene glycol-coated (pegylated) liposomes or ‘‘stealth’’ liposomes have extended biological half-lives since PEG- coating avoids their uptake by RES
- Liposomes prepared with cationic and fusogenic lipids are currently being utilized in gene therapy to delivery DNA into target cells
- The cationoic lipids bind with DNA & fusogenic lipids are able to fuse with cell membranes, allowing the DNA to be introduced into cells.

Microemulsion (lipid microspheres)

- Thermodynamically stable, transparent, low viscosity and spontaneous formation system composed of water, oil, surfactant and/or cosurfactant with an internal droplet size ranging 10- 100 nm. Thus, it is a colloid-sized emulsion droplets
- Used in drug delivery :
  - ➢to solubilise water-insoluble drug substances
  - ➢ for the purposes of controlled & sustained release
  - ➢ for drug targeting

Microspheres:

- Solid, almost spherical particles
- Prepared from natural polymers [gelatin & albumin] or synthetic polymers [polylactic & polyglycolic acid
- Range in size ≈1 to 1000 μm
- Contain dispersed drug in microcrystalline or solution form
- Drug is either totally encapsulated within a distinct capsule wall or is dispersed throughout microsphere

- Incorporation of drugs can be achieved by:
  - ✓entrapment during production (polymerization, gelation, or encapsulation techniques, such as coacervation and phase separation)
  - ✓covalent attachment
  - ✓ionic attachment
- Drug release is controlled by dissolution & diffusion of the drug through the microsphere matrix or the microcapsule wall, or by polymer degradation